EPA Jacket 2517-85

Vol.1

DP #: (317320)

Decision #: 338118

DATA PACKAGE BEAN SHEET

Date: 24-May-2005

(12)

* * * Registration Information * * *

Registration: 2517-IN - SERGEANTS CYPHENOTHRIN + IGR SQUEEZE-ON FOR DOGS

Company: 2517 - SERGEANTS PET CARE PRODUCTS, INC.

Risk Manager: RM 13 - George Larocca - (703) 305-6100 Room# CM-2 206

Risk Manager Reviewer: George Larocca GLAROCCA

Sent Date: 23-Jun-2004 Calculated Due Date: 13-Feb-2007 Edited Due Date:

Type of Registration: Product Registration - Section 3

Action Desc: (R26.4) NEW USE;NON-FOOD;INDOOR;

Ingredients: 129032, Pyriproxyfen(2%)

129013, Cyphenothrin(40%)

* * * Data Package Information * * *

Expedite: ○ Yes ● No Date Sent: 24-May-2005 Due Back:

DP Ingredient: 129013, Cyphenothrin

129032, Pyriproxyfen

DP Title:

CSF Included: ○ Yes ● No Label Included: ○ Yes ● No Parent DP #:

Assigned To		Date In	Date Out	
Organization:	RD / TRB			Last Possible Science Due Date: 13-May-2006
Team Name:	TOX			Science Due Date:
Reviewer Name:	Backus, Byron			Sub-Data Package Due Date:
Contractor Name:				

* * * Studies Sent for Review * * *

* * * Additional Data Package for this Decision * * *

* * * Data Package Instructions * * *

Byron - You completed review of the companion animal safety study for 2517-IN, IL on Nov. 30th and Nov 24th, 2004. Mark Suarez completed review of efficacy data(MRID 46166109) associated with these two products and noted symptoms reported in all dogs in Test Group 2(see attached excerpt). This appears to be inconsistent with what you reported. Mark has electronically sent you a copy of the efficacy study for further consideration.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: November 30, 2004

MEMORANDUM

Subject: EPA File Symbol: 2517-IL SERGEANT'S CYPHENOTHRIN SQUEEZE-ON FOR DOGS
DP Barcode: D305953
Decision No.: 345654
PC Code: 129013 Cyphenothrin (CAS #39515-40-7)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

To: Linda DeLuise/George LaRocca RM 13
Insecticide Branch
Registration Division (7505C)

Applicant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION DECLARATION FROM LABEL:

Active Ingredient(s):	% by wt
Cyphenothrin (CAS #39515-40-7)	40.0%
Inert Ingredients:	60.0%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

> Waiver request [for] acute inhalation; refer to 2517-IN for other studies and companion animal [study].

BACKGROUND:

The data cited and previously reviewed (for EPA File Symbol 2517-IN) includes an acute oral LD_{50} study (rat, up-and-down procedure, defaulting to an acute toxic class procedure, MRID 46166103); acute dermal LD_{50} study (rat; MRID 46166104); primary eye irritation study (rabbit; MRID 46166105); primary dermal irritation study (rabbit; 46166106) and a dermal sensitization study (guinea pig; 46166107), as well as a companion animal safety study in dogs (MRID 46166108). The five acute toxicity studies were conducted at Product Safety Labs, New Jersey. The companion animal safety study was conducted at Stillmeadow, Inc. In addition, there is a waiver request for an inhalation study. All studies were conducted on Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL, containing 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar.

RECOMMENDATIONS:

1. The companion animal (dog) safety study in MRID 46166108 has been reviewed and has been classified as acceptable for puppies (12 weeks and older) and adult dogs. It is concluded that there is an adequate margin of safety (at least 5X) between the exposure associated with the proposed use level for this formulation in dogs, and that at which significant adverse systemic effects (not seen in this study, but which might include ear twitching, muscle tremors, drooling) may occur. For dermal effects an effect was observed in one puppy in Group III (treated at essentially a 7.5X dose level), but in none of the other dogs (including the puppies in Group II, dosed at 1.5X) indicating a reasonably low potential for this effect in dogs treated at the proposed use level.

2. It is noted that the test material in the companion animal (dog) safety study was supplied in (and applied from) unidose 1.5 mL ampules. However, the report states that the mean volume delivered from a single 1.5 mL ampule was 1.17 mL, and the registrant is proposing packaging this product in 3.0 and 4.5 (as well as 1.0 and 1.5) mL tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2 x 1.17) mL and the 4.5 mL tubes deliver no more than 3.51 (3 x 1.17) mL.

3. The five acute toxicity studies have been reviewed and classified as acceptable. In addition, TRB has no objection to the registrant's waiver request for an acute

inhalation study, based on the product form (a liquid), its proposed packaging (1.0, 1.5, 3.0 or 4.5 mL tubes or ampules), the method of application (as a spot-on or stripe-on to the dog's back), and the relatively low inhalation toxicity of technical Cyphenothrin (one report from the open literature gives a rat LC50 of 1.85 mg/L, or EPA toxicity category III; extrapolating from this the inhalation LC50 value for a 40% Cyphenothrin-60% inert product would then be greater than 4 mg/L, or EPA toxicity category IV by this exposure route).

4. Based on the results of the acute toxicity studies, the following is the acute toxicity profile for EPA File Symbol: 2517-IL SERGEANT'S CYPHENOTHRIN SQUEEZE-ON FOR DOGS. The signal word of the product would be CAUTION, as proposed by the registrant:

Study Type	Tox. Cat.	Classification & MRID #
Acute Oral LD_{50} (rat)	III	Acceptable (#46166103)
Acute Dermal LD_{50} (rat)	III	Acceptable (#46166104)
Acute Inhalation LC_{50}	IV	Waived
Primary Eye Irritation (rabbit)	III	Acceptable (#46166105)
Primary Dermal Irritation (rabbit)	IV	Acceptable (#46166106)
Dermal Sensitization (guinea pig)	Negative	Acceptable (#46166107)

5. Based on the acute toxicity profile and proposed uses, the following is the precautionary labeling for this product, as obtained from the Label Review System:

PRODUCT ID #: **002517-00085**

PRODUCT NAME: **SERGEANT'S CYPHENOTHRIN SQUEEZE-ON FOR DOGS**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Harmful if swallowed or absorbed through skin.. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling.

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical advice.

Reviewer: Byron T. Backus, Ph.D. Date: November 19, 2004
Risk Manager (EPA): 13

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IL Sergeant's Cyphenothrin Squeeze-On for Dogs (although this product does not contain either Nylar or Methoprene) with a label declaration of: Cyphenothrin 40.0%.

CITATION: Moore, G. (2003) Acute Oral Toxicity Up and Down Procedure in Rats: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13320, P320/UDP. Unpublished study prepared by Product Safety Labs, Food Product Laboratory and Silliker Laboratories of New Jersey, Inc. 16 p. Study Completion Date: May 20, 2003. MRID 46166103.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46166103), conducted using the up-and-down procedure but defaulting to the acute toxic class method, Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Gokilaht (Cyphenothrin), 3.0% Methoprene and 2.00% Nylar was administered by oral gavage at 2000 mg/kg to a single Sprague-Dawley derived 9-week-old albino fasted (overnight) female rat. When this rat survived, four additional fasted (overnight) female rats of the same strain, age, body weight range (164-182 g) and source (Ace Animals, Inc., Boyertown, PA) were also dosed at 2000 mg/kg.

On the day of dosage rats were observed for several hours for mortality and signs of gross toxicity for several hours post-dosing. They were then observed at least once a day for the remainder of the 14-day observation period.

On the day of dosage rats were observed at least 3 times within the first 4 hours after dosing for clinical signs of toxicity and mortality and then at least once daily for the remainder of the 14-day observation period. Individual body weights were recorded just prior to dosing (Day 0) and on days 7 and 14. Individual body weights were recorded predosing and on days 7 and 14.

Two rats died within 24 hours of dosage with no clinical signs observed prior to death. Two rats which survived showed reduced fecal volume, ventral staining and hypoactivity, with recovery by Day 4. All survivors gained weight in the period from Day 0 (predose) to Day 7 and again from Day 7 to 14.

Postmortem necropsy findings in the rats which died showed discoloration of the lungs and intestines and fluid filled stomachs. Gross necropsy findings in rats surviving to terminal sacrifice were unremarkable.

Estimated Oral LD_{50} in female rats > 2000 mg/kg.

EPA File Symbol 2517-IL Sergeant's Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA Toxicity Category III based on the results of testing of a liquid with a specific gravity of 1.061 g/mL containing 40% Cyphenothrin, 2% Pyriproxyfen (Nylar) and 3% Methoprene, based on the observed LD_{50} (>2000 mg/kg) in female rats.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 16), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Friday, October 15, 2004, 4:37:11 PM
Data file name: Cyphenothrin-IGR.dat
Last modified: 10/15/2004 4:37:11 PM

Test/Substance: Cyphenothrin-IGR
Test type: Limit Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	8040	2000	O	O
2	8198	2000	O	O
3	8239	2000	O	O
4	8372	2000	X	X
5	9407	2000	X	X

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
2000	3	2	5
All Doses	3	2	5

Statistical Estimates:

The LD50 is greater than 2000 mg/kg.

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	-	2/5	-

Statistics - Not necessary to compute the oral LD_{50}.

A. Mortality - As noted in the table above.

B. Clinical observations - Two rats died within 24 hours of dosage with no clinical signs observed prior to death. Two rats which survived showed reduced fecal volume, ventral staining and hypoactivity, with recovery by Day 4. All survivors gained weight in the period from Day 0 (predose) to Day 7 and again from Day 7 to 14.

C. Gross Necropsy - Postmortem necropsy findings in the rats which died showed discoloration of the lungs and intestines and fluid filled stomachs. Gross necropsy findings in rats surviving to terminal sacrifice were unremarkable.

D. Reviewer's Conclusions: The study is acceptable. EPA File Symbol 2517-IL Sergeant's Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA toxicity category III for oral toxicity based on the results from testing a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 40% Cyphenothrin, 2% Pyriproxyfen (Nylar) and 3% Methoprene based on the observed LD_{50} (>2000 mg/kg) in female rats.

E. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 22, 2004
Risk Manager (EPA): 13

STUDY TYPE: Acute Dermal Toxicity - Wistar rats - OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IL Sergeant's Cyphenothrin Squeeze-On for Dogs (although this product does not contain either Nylar or Methoprene) with a label declaration of Cyphenothrin 40.0%.

CITATION: Moore, G. (2003) Acute Dermal Toxicity Study in Rats - Limit Test: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13321, P322. Unpublished study prepared by Product Safety Labs, Food Product Laboratory and Silliker Laboratories of New Jersey, Inc. 16 p. Study Completion Date: May 20, 2003. MRID 46166104.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID #46166104), a group (5M & 5F) of Sprague-Dawley derived albino rats (source: Ace Animals, Inc., Boyertown, PA; Males: 300-318 g; Females: 178-204 g; young adult [indicated by body weight data]) were dermally exposed (approximately 10% of body surface) for 24 hrs to 2000 mg/kg of undiluted Cyphenothrin-IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen). The test material was held in contact by a gauze pad and Durapore tape.

Rats were observed several times after application on day 0 and once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing (day 0) and on days 7 and 14.

There was no mortality and there were no signs of systemic toxicity. Three males showed some dermal irritation (erythema and/or edema) with clearing by day 2. All rats gained weight from day 0 to 7 and from day 7 to 14.

No gross abnormalities were observed at post-sacrifice necropsy.

Dermal LD_{50} Males > 2000 mg/kg (0/5 died)
Females > 2000 mg/kg (0/5 died)
Combined > 2000 mg/kg (0/10 died)

Cyphenothrin-IGR Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA toxicity category III in terms of dermal toxicity based on the testing of Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared, a clear, light yellow liquid with a

specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar with a rat LD_{50} > 2000 mg/kg,

This acute dermal study is classified as acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 16), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

Statistics - Not necessary to compute the dermal LD_{50}.

A. Mortality - None, as noted in the table above.

B. Clinical observations - There were no signs of systemic toxicity. Three males showed some dermal irritation (erythema and/or edema) with clearing by day 2. All rats gained weight from day 0 to 7 and from day 7 to 14.

C. Gross Necropsy - No gross abnormalities were observed at post-sacrifice necropsy.

D. Reviewer's Conclusions: The study is acceptable. Cyphenothrin-IGR Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA toxicity category III in terms of dermal toxicity based on the testing of Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar with a rat LD_{50} > 2000 mg/kg.

E. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 23, 2004
Risk Manager (EPA): 13

STUDY TYPE: Primary Eye Irritation - NZW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IN Sergeant's Cyphenothrin Squeeze-On for Dogs (although this product does not contain Methoprene or Pyriproxyfen) with a label declaration of Cyphenothrin 40.0%.

CITATION: Moore, G. (2003) Primary Eye Irritation Study in Rabbits: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13322, P324. Unpublished study prepared by Product Safety Labs, Food Products Laboratory and Silliker Laboratories of New Jersey, Inc. 17 p. Study Completion Date: May 20, 2003. MRID 46166105.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46166105), 0.1 mL of undiluted Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen), was instilled into the conjunctival sac of one eye of each of 3 adult New Zealand White Rabbits (weights: not reported; ages: young adult; source: Davidson's Mill Farm, South Brunswick, NJ), with observations and scoring at 1, 24, 48 and 72 hours after instillation.

No corneal opacity was observed (with 2% ophthalmic fluorescein sodium used at 24 hours to verify the absence of corneal opacity at that reading). 3/3 eyes were positive for conjunctival redness (score of 2) at 1 and 24 hours. All eyes were completely clear (all scores zero) at 72 hours.

Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA toxicity category III for eye irritation, based on the findings (presence of grade 2 conjunctival redness in 3/3 eyes at 24 hrs with subsequent clearing by 72 hrs) from a study with Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen).

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 17), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested			
	1 hr	24 hrs[2]	48 hrs	72 hrs
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness[1]	3/3	3/3	0/3	0/3
Chemosis[1]	0/3	0/3	0/3	0/3
Discharge[1]	3/3	0/3	0/3	0/3

[1]Score of 2 or more considered positive
[2]Fluorescein staining was used to verify the absence of corneal opacity.

A. **Observations** - No systemic effects were observed. 3/3 eyes were positive for conjunctival redness (score of 2) at 1 and 24 hours. All eyes were completely clear (all scores zero) at 72 hours.

B. **Reviewer's Conclusions:** The study adequately defines a Toxicity Category III hazard potential in terms of eye exposure potential for Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) based on the findings of this study conducted on Cyphenothrin + IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen).

C. **Deficiencies** - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 23, 2004
Risk Manager (EPA): 13

STUDY TYPE: Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IL Sergeant's Cyphenothrin Squeeze-On for Dogs (although this product does not contain Methoprene or Pyriproxyfen) with a label declaration of Cyphenothrin 40.0%.

CITATION: Moore, G. (2003) Primary Skin Irritation Study in Rabbits: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13323, P326. Unpublished study prepared by Product Safety Labs, Food Products Laboratory and Silliker Laboratories of New Jersey, Inc. 17 p. Study Completion Date: May 20, 2003. MRID 46166106.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46166106), 0.5 mL aliquots of undiluted Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen), were applied to dermal sites on each of 3 (2M & 1F) young adult New Zealand White albino rabbits (source: Davidson's Mill Farm, South Brunswick, NJ) with 4-hour semioccluded exposure.

After 4 hours, the gauze patch and holding tape were removed. The test sites were scored (Draize) at 1, 24, 48 and 72 hrs and at 7 and 10 days.

No edema was observed (all scores for edema were zero). All sites scored one for erythema at 1 hour and 2 at 24, 48 and 72 hours. One site scored 2 for erythema on day 7 while the other two scored 1. All scores were zero on day 10. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.75.

Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA Toxicity Category IV for dermal irritation effects, based on the findings (PII of 1.75 and relatively low score (grade 2, characterized as well-defined) for erythema at 72 hrs [EPA Toxicity Category III would be characterized by moderate or grade 3 erythema at 72 hrs] following 4-hr semi-occluded exposure) from a study conducted on Cyphenothrin + IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen).

This study is classified as acceptable. It does satisfy the guideline requirement for a primary

dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 17), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

A. Observations - No edema was observed (all scores for edema were zero). All sites scored one for erythema at 1 hour and 2 at 24, 48 and 72 hours. One site scored 2 for erythema on day 7 while the other two scored 1. All scores were zero on day 10. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.75.

B. Results - The PII (average of t, 24, 48 and 72-hour scores) = 1.75 The mean irritation score on day 3 was 2.0 (erythema: 2.0; edema: 0.0).

C. Reviewer's Conclusions - Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) is in EPA Toxicity Category IV in terms of dermal irritation based on the results from testing with Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen).

D. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 23, 2004
Product Manager (EPA): 13

STUDY TYPE: Dermal Sensitization - albino Guinea Pig; OPPTS 870.2600; OECD 406, 429

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IL Sergeant's Cyphenothrin Squeeze-On for Dogs (although this product does not contain Methoprene or Nylar) with a label declaration of Cyphenothrin 40.0%.

CITATION: Moore, G. (2003) Dermal Sensitization Study in Guinea Pigs: Buehler Method: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13324, P328. Unpublished study prepared by Product Safety Labs, Food Products Laboratory and Silliker Laboratories of New Jersey, Inc. 25 p. Study Completion Date: May 20, 2003. MRID 46166107.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46166107) with Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen), a group of 20M Hartley albino guinea pigs (373-428 g; young adult; source: Elm Hill Breeding Labs, Chelmsford, MA) were each dermally exposed (6 hours) to a 0.4 mL aliquot of test material on a once-a-week basis for 3 consecutive weeks. After a two week rest period they were then dermally challenged with 0.4 mL of a 75% w/w mixture of the test material in mineral oil at a previously unexposed site. An additional 10 previously unexposed male guinea pigs received were similarly treated. Challenge sites on all 30 guinea pigs were evaluated and scored for erythema at 24 and 48 hours after the application.

Following challenge, 7/20 previously exposed guinea pigs showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours. 4/10 controls showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours.

The report includes results from a positive control study (PSL Study #12371) which was conducted with technical (85%) alpha-Hexylcinnamaldehyde and completed on August 15, 2002. The results (3/10 previously exposed, 0/5 naive control guinea pigs showing a positive response at challenge) were appropriate. The study dates for the testing with Cyphenothrin-IGR Squeeze-On for Dogs were from March 13 to April 11, 2003. While slightly outside the 6-month period indicated in the Guidelines, it is concluded the overall study findings are acceptable.

In this study **there were no indications that Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is a dermal sensitizer.**

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406, 429) in the Guinea pig.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 25), and [No] Data Confidentiality (p. 2) statements were provided.

I. PROCEDURE

A. Induction - Each of 20 male Hartley albino guinea pigs was treated once a week for 3 consecutive weeks to a 6-hour exposure to 0.4 mL undiluted Cyphenothrin-IGR Squeeze-On for Dogs.

B. Challenge - Twenty-seven days after the first induction exposure 0.4 mL of a 75% w/w mixture of the test material in mineral oil was applied to a naive site on the right side of each guinea pig at a previously unexposed site. These sites were evaluated and scored for erythema at 24 and 48 hours after the challenge application.

C. Naive Controls - At the time the 20 previously induced guinea pigs were challenged, 10 previously unexposed (negative control) guinea pigs were similarly challenged.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Following challenge, 7/20 previously exposed guinea pigs showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours. 4/10 controls showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours.

B. Positive control - The report includes results from a positive control study (PSL Study #12371) which was conducted with technical (85%) alpha-Hexylcinnamaldehyde and completed on August 15, 2002. The results (3/10 previously exposed, 0/5 naive control guinea pigs showing a positive response at challenge) were appropriate. The study dates for the testing with Cyphenothrin-IGR Squeeze-On for Dogs were from March 13 to April 11, 2003. While slightly outside the 6-month period indicated in the Guidelines, it is concluded the overall study findings are acceptable.

C. Reviewer's Conclusions: Cyphenothrin Squeeze-On for Dogs (containing 40% Cyphenothrin) is not a dermal sensitizer, based on the results from testing Cyphenothrin + IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is not a dermal sensitizer.

D. Deficiencies - The final date for the cited positive control study is approximately 7 months before the initiation of this study. However, TRB can accept the results of this study.

EPA Primary Reviewer: Byron T. Backus, Ph.D. Signature: _____
Technical Review Branch, Registration Division (7505C) Date_____
EPA Secondary Reviewer: William Dykstra, Ph.D. Signature: _____
Health Effects Division (7509C) Date_____

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety - Dogs OPPTS 870.7200

PC CODES: 129013 (Cyphenothrin), 129032 (Nylar), 105401 (Methoprene)
DP BARCODE: D305948 **RISK MANAGER:** (EPA): 13 **DECISION NO.:**338118

PRODUCT AND TEST MATERIAL: Cyphenothrin-IGR Spot-on for Dogs. [EPA File Symbol 2517-IN]; a liquid labeled "Gokilaht Spot-On w/IGR's (2824) 40.00% RS-Gokilaht; 3.00% S-Methoprene; 2.00% Nylar." According to a certificate of analysis (p. 47 of MRID 46166108) the formulation contained 39.87% Gokilaht, 3.00% S-Methoprene and 2.00% Nylar. Packaged in unidose ampules containing 1.5 mL product.

CITATION: Kuhn, J. (2003) Companion Animal Safety Study in Dogs: Cyphenothrin-IGR Spot-on for Dogs. Final Report. Project Number 7650/03. Unpublished study prepared by Stillmeadow, Inc. and Miller, Thomas A. 53 p. Study Completion Date: 20 October 2003. MRID 46166108.

SPONSOR: Sergeant's Pet Care Products, Inc. Omaha, NE 68130-1703.

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 46166108), groups of 12 dogs (from 5 to 9 males in each group) with each group including three 12-week old puppies weighing 4.1-6.1 kg, 2 or 3 dogs weighing 6.8-15 kg, 3 or 4 dogs weighing 15.1-29.5 kg, and 3 weighing >29.5 kg) were dosed with: 1) the amount of vehicle contained in a single dose (Group I, controls); 2) at 1X the label use directions (except for puppies, which were dosed at 1.5X) in Group II, and 3) at 5X the label use directions (except for puppies, which were dosed at 7.5X) in Group III. Group III dogs were treated five times with one hour between each treatment.

The test material was supplied in unidose 1.5 mL ampules. However, the report states that the mean volume delivered from one of these ampules was 1.17 mL. One dose for puppies consisted of material from a single 1.5 mL ampule (the proposed label states that dogs weighing less than 15 lbs [= 6.8 kg] are to be treated with 1.0 mL), for dogs weighing 15-33 lbs (6.8-15 kg) it was 1.5 mL, for dogs weighing 15.1-29.5 kg it was the contents of two 1.5 mL ampules (the proposed label says two 1.5 mL or one 3.0 mL ampule), and for dogs weighing >29.5 kg it was three 1.5 mL ampules (the proposed label says three 1.5 mL or one 4.5 mL ampules). The control material was supplied in bulk and placebo controls were treated with this formulation (without actives) at the rate of 55.13% of the active product dose volumes.

Administration was according to the proposed label directions and involved application of the test substance (or control vehicle) to the skin in a line along the spine starting at the back of the neck. Label directions specify application of the product as a spot-on or stripe treatment between the shoulder blades to dogs weighing up to 15 kgs. For dogs weighing between 15 and 29.5 kg application would be as a spot-on or stripe treatment at two sites on the back, one

between the shoulder blade and one directly in front of the base of the tail. For >29.5 kg the contents of one 1.5 mL ampule would be applied to the back as a spot-on or stripe between the shoulder, and the contents of the other two 1.5 mL ampules would be applied as a stripe on the back in front of the base of the tail.

Each dog in Groups I and II was observed at 1, 2, 3 and 4 hours following treatment on Day 0. Group III dogs were also observed "between the hourly dosings" (1, 2, 3, 4, 5, 6, 7 and 8 hours after the first treatment). All dogs were then observed twice (a.m. and p.m.) on Days 1-15.

Individual body weights were determined on Days -7, -3, 7 and 14. Individual food consumption was determined on a daily basis from Day -7 through Day 15 by measuring the amount of food given to each dog in the morning and subtracting the amount left at the end of the day. Blood samples were taken on Days -7 and 1 following overnight fasts.

Possible systemic effects related to exposure to the test material included ocular discharge and salivation. In the immediate period following treatment, ocular discharge was observed in one Group II dog (a puppy) at 4 hours post-dose, and in 4 Group III dogs (including all three puppies). Salivation (mostly very slight, but in some cases moderate) was observed in five Group III dogs (including 1/3 puppies), and was observed (very slight) in one adult 32.2 kg dog at 1 hour postdose (so at this time this dog had presumably been treated with only 1 or 2 applications of test material). Salivation was seen in another Group III adult starting at 3 hours, and in two additional Group III adults starting at 4 hours. During the subsequent 15-day observation period, ocular discharge was frequently observed (including continuously from day 10 to 15) in one control puppy, in none of the Group II (1X) dogs, and in one Group III puppy (days 1-2) and one Group III adult (days 1-6, then again on Days 13-15); both of these Group III animals had also shown ocular discharge in the period immediately following the first treatment. Salivation was observed in one Group III adult male at the AM observation on Day 1 (this dog had also showed salivation during the 8-hour period following the first treatment). One Group III male puppy showed a lesion (or lesions) on both sides of the shoulder (presumably at or near the application site) from Day 5 through 15, and was observed to scratch this area frequently.

Group III adults showed a mean weight loss between days -3 and +7. The incidences of adult dogs showing weight losses between days -3 and +7 were: Group I: 3/9; Group II: 4/9; Group III: 6/9. It is concluded then that for adult dogs exposure to a 5X dosage of test material was associated with a slight mean weight decrease in the period from Day -3 to Day 7.

While Group I puppies showed a greater mean weight gain in the period from Day -3 to +7 than Groups II and III, their mean weight gain/day in the subsequent period from Day 7 to 14 (0.053 kg/day) was comparable to the mean weight gains from Day -3 to +7 for Groups II (0.033 kg/day) and III (0.047 kg/day). Group III puppies also showed a greater mean weight gain in the period from Day -3 to 7 than did Group II puppies. There is no indication then that exposure to the test material affected body weight gain in puppies.

Puppies in Groups II and III showed lower mean food consumption values on Days 0 and 1 relative to their controls. This has to be considered as treatment-related. A similar effect in the adults was not evident.

No effects were noted on hematological or clinical chemistry parameters.

While the Guidelines for this type of study state that the targeted adequate margin of safety is 5X, it is also stated that: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)." The test material was not tested at 3X and effects were noted at 5X. However, the

effects noted at 5X, including ocular discharge (also noted in one puppy dosed at what was essentially 1.5X) and salivation were minimal (most occurrences of both ocular discharge and salivation were described as "very slight.") and reasonably transient. It is noteworthy that no systemic neurological signs (such as tremors or ataxia) were observed, and the salivation may have been due to ingestion of small amounts of test material from licking or biting the application area. In addition, the performing laboratory has demonstrated in the past extremely meticulous reporting of observational data in companion animal safety studies, and it is quite likely that these observations would not have been reported from some of the other laboratories which conduct this type of study.

For local dermal effects, one puppy treated at what was essentially a 7.5X dose level showed subsequent shoulder lesions and was noted to scratch this area frequently. Dermal exposure to pyrethroids can cause a burning and/or itching sensation at the application site, and this has to be considered an effect (unless the registrant can provide additional information demonstrating otherwise). However, this was an isolated case, and the three adult dogs treated with 3 unit doses/application with a total of 5 applications (for a total of fifteen 1.5-mL ampules in all) did not show a similar response.

However, one area of concern is that the 1.5 mL ampules (the only size tested in this study) delivered only an average of only 1.17 mL of test material, and the registrant is proposing packaging this product in 3.0 and 4.5 mL (as well as 1.0 and 1.5 mL) tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2 x 1.17) mL and the 4.5 mL tubes deliver no more than 3.51 (3 x 1.17) mL.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for puppies (12 weeks and older) and adult dogs. **It is concluded that there is an adequate margin of safety (at least 5X) between the exposure associated with the proposed use level for this formulation in dogs and that at which significant adverse systemic effects (not seen in this study, but which might include ear twitching, muscle tremors, drooling) may occur.** For dermal effects an effect was observed in one puppy in Group III (treated at essentially a 7.5X dose level), but in none of the other dogs (including the puppies in Group II), indicating a reasonably low potential for this effect in dogs treated at the proposed use level.

COMPLIANCE: Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: Cyphenothrin-IGR Spot-on for Dogs, with a label declaration for active ingredients of RS-Gokilaht [=Cyphenothrin] (40.00%) , S-Methoprene (3.00%), and Nylar (2.00%). According to a certificate of analysis on p. 47 of MRID 46166108 the respective analytical values were 39.87%, 3.00% and 2.00%. Packaged in unit dose ampules containing 1.5 mL.
   Description: A liquid;
   Lot No.: #1683B
   Storage: Room Temperature

2. Administration: Topical (spot-on)

3. Vehicle control: X-5699-03 (Placebo Control); From Study 0310: Lot #03390A0100. liquid which was stored at room temperature.

4. Test animals
Species: Dog
Breed: From p. 9 of MRID 46166108: "Beagles and other breeds..."
Ages and weights at study initiation: "Animals were at least 3 months old at dosing. There were 3 animals from each group in each of the following weight ranges: <15, 15-33, 34-65 and >65 pounds (<6.8, 6.8-15, 15.1-29.5 and >29.5 kg). All dogs less than 15 pounds were pups that were 12 weeks old at dosing." [Note by reviewer: The alkaline phosphatase measurments from Dog 2854F (controls), 3085M (Group II) and 2156M (Group III) were relatively high - refer to pp. 32-34 - suggesting these were fairly young dogs too].
Sources: Butler Farms (Clyde, NY), Martin Creek Kennels (Williford, AR), Ridglan Farms (Mt. Horeb, WI) and STILLMEADOW, Inc.
Housing: Individually in kennels measuring 3' x 5.5'.
Diet: PMI Canine High Density Diet 5L18.
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 22° ± 3°C
Humidity: 30 - 70%
Air changes: 10 - 12/hr
Photoperiod: 12 hr dark/12 hr light
Acclimation period: 2 weeks

II. STUDY DESIGN

A. IN LIFE DATES

From the report cover: study initiation date: 13 August 2003; study completion date: 20 October 2003.

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

There were a total of 12 dogs per dosage group. Group 1 (1X vehicle; note: observation schedule on p. 16 of MRID 46166108 is the same for Groups 1 and 2, consistent with a single application of placebo on dogs in Group 1) consisted of 9 males and 3 females; Group II (1X) consisted of 5 males and 7 females, and Group III (5X) consisted of 8 males and 4 females. Assignment was on the basis of weight. From p. 10 of MRID 46166108: "Animals selected for testing were randomly assigned to three groups... Since there were three dose sizes (based on animal body weight) to be used in each treatment group, three dogs of each weight range were included in each group. The weight ranges were <15, 15-33, 34-65 and >65 pounds (<6.6, 6.8-15, 15.1-29.5 and >29.5 kg). The dogs <15 pounds were 3-month old puppies."

From p. 10 of MRID 46166108: "The test substance and placebo were applied to the skin in a line along the spine starting at the back of the neck. The test substance was supplied in unit dose plastic tubes, each containing 1.5 mL and were administered to each animal according to its body weight. The placebo control substance was provided in bulk. On Day 0, a label dose (1X) of the test substance was administered to each Group II animal according to body weight. Group III animals received the test substance at five times the label dose (5X) administered as single doses once every hour for 5 hours. The single dose volumes were: dogs <15 pounds, 1.5 mL (one unit dose); dogs 13 [15?]-33 pounds, 1.5 mL (one unit dose); dogs 34-65 pounds, 3 mL (two unit doses); and dogs >65 pounds, 4.5 mL (three unit doses). Group I was treated with the placebo control material in a volume equivalent to that of the normal label dose of the test substance less the volume of that dose that was occupied by the active ingredients [or approximately

55% of a normal 1X dose volume]..."

TABLE 1. Study design							
Group & Weight Range (kg)		Number of dogs or puppies		Cumulative Dose/dog			Number of applications
		Male	Female	Total/Dog	Mean mL/kg	Mean Dosage Cyphenothrin (mg/kg)[d]	
I (control)	<6.6[a]	3	0	0.83 mL[b]	0.16[b]	0	1
	6.8-15	1	1	0.83 mL[b]	0.08[b]	0	
	t5.1-29.5	2	2	1.65 mL[b]	0.09[b]	0	
	>29.5	3	0	2.48 mL[b]	0.07[b]	0	
II (1X)	<6.6[a]	t	2	1.17 mL[c]	0.28[c]	112[d] [121][e]	1
	6.8-15	1	2	1.17 mL[c]	0.09[c]	36[d] [39][e]	
	15.1-29.5	1	2	2.34 mL[c]	0.12[c]	48[d] [52][e]	
	>29.5	2	1	3.51 mL[c]	0.11[c]	42[d] [45][e]	
III (5X)	<6.6[a]	1	2	5.85 mL[c]	1.26[c]	503[d] [543][e]	5
	6.8-15	0	2	5.85 mL[c]	0.51[c]	207[d] [224][e]	
	15.1-29.5	3	1	11.7 mL[c]	0.64[c]	255[d] [275][e]	
	>29.5	3	0	t7.55 mL[c]	0.50[c]	199[d] [2 t5][e]	

Data calculated from information on p. 14-15 in MRID 46166108.
[a] Puppies
[b] Placebo
[c] Test material (with actives); amount delivered based on 1.17 mL/application.
[d] Based on a specific gravity for the test material of 1.00 g/mL (consistent with the calculations for dosage as reported on pp. 14-15 of MRID 46166108) and based on 1.17 mL delivered/tube.
[e] Based on a specific gravity of 1.08 g/mL
Note: According to the CSF the specific gravity of the proposed product is about 1.08; assuming the product contains 40% Cyphenothrin then 1.5 mL would be 1.62 g and would contain 648 mg of Cyphenothrin. The calculations of dosage of Cyphenothrin in the report (see p. 14-15 of MRID 46166108) appear to be based on a specific gravity for the proposed product of about 1.00. Example: Dog 3067 F weighing 4.2 kg received one 1.5 mL dose of the product and this is reported as a dosage of 142 mg/kg Cyphenothrin. 142 mg/kg x 4.2 kg = 596.4 mg; dividing this by 0.3987 (the analytical percentage) gives 1496 mg (= 1.496 g) total product applied. However, in Appendix G (see p. 52 of MRID 46166 t08) it is stated that the unit dose containers did not deliver the entire target dose of 1.5 mL, as there was a mean delivered volume of 1.17 mL. A statement in Appendix G ("...5X dose rates ranged from 494 to 630 mg/kg for the smallest subjects.") is consistent with delivery of 1.17 mL/dose and a specific gravity of about 1.08 g/mL.

C. DOSE SELECTION RATIONALE

According to the proposed label this product will be packaged in unidose 1.0, 1.5, 3.0 and 4.5 mL applicator tubes. These correspond to single treatments for dogs weighing 15 lbs and under, 15-33 lbs, 33-66 lbs and >66 lbs. However, in this study, Group 2 (1X) dogs (puppies) weighing less than 15 lbs received 1.5 mL (instead of 1.0 mL), while Group 3 (5X) dogs (puppies) weighing less than 15 lbs received 5 x 1.5 mL = 7.5 mL (instead of 5 x 1.0 mL = 5.0 mL).

D. EXPERIMENTAL DESIGN

From p. 10 of MRID 46166108: "Each animal was observed at 1, 2, 3 and 4 hours following dosing on Day 0 and then twice daily [AM and PM] for the duration of the study. Group III animals were also observed between the hourly dosings. Each animal was examined for signs of any pharmacologic and/or toxicologic effects. Only abnormalities were recorded."

Individual dogs were weighed on Days -7, -3, 7 and 14.

Individual food consumption was measured daily by measuring the amount of food given to each dog in the morning and subtracting the amount of food left at the end of the day.

Baseline blood samples were collected from each dog on Day -7 by jugular venipuncture following an overnight fast. Blood samples were also similarly collected on Day 1.

E. PATHOLOGICAL PARAMETERS

Blood samples were collected on Study Days -7, and 1 by jugular venipuncture following an overnight fast. The CHECKED (X) parameters were examined:

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin (Alb)*
X	Chloride*	X	Blood creatinine (Crea)*
	Magnesium	X	Blood urea nitrogen (BUN)*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin (Glob)*
X	Sodium*	X	Glucose (Gluc)*
		X	Total and direct bilirubin (T Bil & D Bil)*
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase(ALPor ALK)*		Triglycerides
	Cholinesterase(ChE)		Serum protein electrophoresis
	Creatine kinase	X	Albumin/Globulin (A/G) ratio
	Lactic acid dehydrogenase(LDH)		
X	Serum alanine aminotransferase (ALT or SGPT)*		
X	Serum aspartate aminotransferase(AST or SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

The statistical report is found in Appendix G. It consists of a 6-page document (pages 48-53 of MRID 46166108). From p. 51 of MRID 46166108: "The data generated by the test facility...were statistically analyzed by Student's "t" test, assuming equal variances, using the statistical program in Microsoft Excel, version 97-SR-1... Since cyphenothrin is potentially the most toxic component of the product (pyriproxyfen and methoprene are known to be virtually mammalian-inert) cyphenothrin dosage was the focus. To ensure that some of the test subjects were treated at or above the target maximum dose rate of 100 mg of cyphenothrin per kg body weight, the 12-week-old Beagle pups were treated with the next higher unit dose volume. Although weighing between 9 and 11 lb at treatment, for which the proposed label dose rate is one dose of 1 mL, these pups received one 1.5 mL unit dose. To validate the dosage delivered to the principals, the expelled contents of six 1.5 mL unit dose containers were each weighed..." [Note: the report text then refers to Table 1.1, which is not present in the report]. From p. 52 of the report: "The dose validation data (Table 1.1) indicated that the unit dose containers, if filled at the target dose volume of 1.5 mL, were not capable of delivering the entire target volume (mean volume delivered was 1.17 mL).

G. DISPOSITION OF ANIMALS

Not stated. According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

H. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The dose per 1.17 mL application (based on a product specific gravity of 1.08 g/mL) is 1.264 g. Since the test material contained (by analysis) 39.87% Cyphenothrin, 3.00% S-Methoprene and 2.00% Nylar, each 1.17 mL dose then contained 0.504 g (=504 mg) Cyphenothrin, 0.038 g (=38 mg) S-Methoprene and 0.025 g (=25 mg) Nylar. For Group II (1X) mean cumulative Cyphenothrin dosages were: puppies (<6.6 kg): 121 mg/kg; dogs 6.8-15 kg: 39 mg/kg; dogs 15.1-29.5 kg: 52 mg/kg; and dogs >29.5 kg: 45 mg/kg. For Group III (5X) dosages were: puppies (<6.6 kg): 543 mg/kg; dogs 6.8-15 kg: 224 mg/kg; dogs 15.1-29.5 kg: 255 mg/kg; and dogs >29.5 kg: 215 mg/kg. Refer to Table 1 of this DER. B. MORTALITY

There was no mortality, with all dogs surviving the 14-day observation period.

C. CLINICAL SIGNS

In the observation period immediately following treatment, no clinical signs of systemic toxicity were observed in Group I (controls). In Group II (tX) animal 3074 (a male pup weighing 4.1 kg) showed very slight ocular discharge from both eyes at 4 hours post-dose. In Group III (5X) four dogs (including all 3 puppies) showed very slight to moderate ocular discharge from one or both eyes in the period from one hour to 8 hours post-dosing. In addition, five dogs (including one puppy) showed very slight to moderate salivation during this period (in two dogs it was classified as very slight). Very slight salivation occurred in one animal at 1 hour (i.e., presumably following a single dosage of test material), and in two others it was first noted at 3 hours (after 3 application treatments)

Slight to moderate green ocular discharge (both eyes) was observed in one control puppy in the period from Day t to Day 6, and then again in this puppy from Day t0 to Day 15. No ocular discharge was observed in Group II in the period from Day 1 to Day 15. One Group III puppy showed clear ocular discharge from the left eye on Days 1 and 2, while an adult dog showed clear ocular discharge from the left eye from Day t through Day 6, then again from Day 13 through Day t5.

TABLE 2. Adverse Effects Observed in Dogs Treated with Cyphenothrin-IGR Spot-on In the Period Immediately Following Treatment[a]

Parameter	Group I (Control)	Group II (1X)	Group III (5X)
Ocular discharge - one or both eyes in the immediate post-dosing period	0[0]	1[1/48]	4[12/96]
Salivation	0[0]	0[0]	5[18/96]
Soft stool	0[0]	0	2[2/96]
Spiked greasy hair at application site in the immediate post-dosing period	0[0]	2]2/48]	0]0]

[a]Data taken from Table 2 (p. 15) of MRID 46166108.

From p. t1 of MRID 46 t66 t08: "Five of the Group II [1X] animals exhibited greasy spiked fur and/or white deposits at the dose site through Day 3. The only other observation noted in this group was moderate white foamy vomit in one dog on Day 8. In Group III, greasy and/or spiked fur and/or white deposits were seen through Day 1 in two dogs, through Day 3 in three dogs, through Day 6 in three dogs and [from Day 5] through Day 15 in one dog. Other observations included slight clear ocular discharge through Day 2 and shoulder lesions through Day t5 in one animal (the dog was observed to scratch the irritated area frequently), and slight to moderate diarrhea on Days 3 and 4 in another animal. Another dog had very slight to moderate clear ocular discharge through study termination with slight to moderate redness around the eye on Days 3-6. One dog exhibited slight salivation on Day 1 and moderate diarrhea on Day 14, and another had a lesion on the back on Days 7-t5."

The Group III dog with the lesions on the shoulder (from p. 18: "both sides") from Day 5 through 15 was 3070M (a male puppy), treated with five 1.5 mL applications, while the Group III dog with the lesion on the back (Days 7-15) was 2853F (a female adult) also treated with five 1.5 mL applications.

D. BODY WEIGHT AND WEIGHT GAIN

From p. 12 of MRID 46166108: "The average weight gain[s] for Groups I, II and III were 1.1, 1.0 and 0.6 kilograms, respectively. There were no significant differences among groups, and no dose related responses."

The values in Table 3 are calculated from individual body weight data (p. 14-15 of MRID 46166108):

TABLE 3. Mean Body Weights for Dogs by Group

Group	kg ± S.D.				Mean Wt change Day -3 to 7	Mean Wt change Day -3 to 14
	Day -7	Day -3	Day 7	Day 14	kg ± S.D.	kg ± S.D.
I (Controls) puppies	4.63 ± 0.50	5.07 ± 0.93	6.13 ± 1.01	6.50 ± 1.10	1.07 ± 0.15	1.43 ± 0.31
I (Controls) adults	21.87 ± 9.93	22.34 ± 10.26	22.86 ± 10.90	23.31 ± 11.15	0.51 ± 0.87	0.97 ± 1.00
II (1X) puppies	4.80 ± 1.14	4.17 ± 0.06	4.50 ± 0.10	4.97 ± 0.31	0.33 ± 0.15	0.80 ± 0.36
II (1X) adults	21.64 ± 9.61	21.90 ± 9.16	22.53 ± 10.29	22.91 ± 10.29	0.41 ± 1.36	1.01 ± 1.61
III (5X) puppies	4.67 ± 0.71	4.63 ± 0.57	5.10 ± 0.70	5.63 ± 0.50	0.47 ± 0.15	1.00 ± 0.10
III (5X) adults	22.18 ± 10.00	22.38 ± 10.35	22.18 ± 10.40	22.86 ± 10.68	-0.20 ± 0.32	0.48 ± 0.58

Values calculated from data on p. 14 and 15 of MRID 46166108.

The possibility exists that there was a switch of puppies (or their bodyweights) as pup 3073M (assigned to controls) weighed 4.1 kg on day -7 but 6.1 kg on day -3, while pup 3074M (assigned to Group II or 1X) weighed 6.1 kg on day -7 but 4.1 kg on day -3. However, because this switch would have occurred before the dogs were treated, there would have been no impact on the study results.

The only group in which adults showed a mean weight loss between days -3 and +7 was Group III. The incidences of adult dogs showing weight losses between days -3 and +7 were the following: Group I: 3/9; Group II: 4/9: Group III: 6/9. It is concluded then that for adult dogs exposure to a 5X dosage of test material was associated with a slight mean weight decrease in the period from Day -3 to Day 7.

While Group I puppies showed a greater mean weight gain in the period from Day -3 to +7 than Groups II and III, their mean weight gain/day in the subsequent period from Day 7 to 14 (0.053 kg/day) was comparable to the mean weight gains from Day -3 to +7 for Groups II (0.033 kg/day) and III (0.047 kg/day). Group III puppies also showed a greater mean weight gain in the period from Day -3 to 7 than did Group II puppies. There is no indication then that exposure to the test material affected body weight gain in puppies.

TABLE 4. Mean Body Weight Gains for Puppies				
	Day -3 to +7	Day -3	Mean Pup Wt. Gain kg/Day Day -3 to +7	Mean Pup Wt. Gain kg/Day Day 7 to 14
I (Controls) puppies	1.07 ± 0.15	0.37 ± 0.15	0.107	0.053
II (1X) puppies	0.33 ± 0.15	0.47 ± 0.21	0.033	0.067
III (5X) puppies	0.47 ± 0.15	0.53 ± 0.25	0.047	0.076

Values calculated from data on p. 14 and 15 of MRID 46166108.

E. FOOD CONSUMPTION

Puppies in Groups II and III showed lower mean food consumption values on Days 0 and 1 relative to their controls. This has to be considered as treatment-related. A similar effect in the adults was not evident.

TABLE 5. Mean Diet ± S.D. (g) Consumed by Dog/Group by Day							
Group	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
I (Controls) puppies	227 ± 40	267 ± 14	263 ± 17	279 ± 27	315 ± 27	252 ± 41	275 ± 0
I (Controls) adults	431 ± 129	475 ± 131	525 ± 110	496 ± 138	504 ± 166	313 ± 173	496 ± t46
II (1X) puppies	193 ± 7	122 ± 3	89 ± 17	239 ± 45	200 ± 81	165 ± 11	209 ± 15
II (1X) adults	384 ± 218	387 ± 202	339 ± 248	410 ± 207	435 ± 216	310 ± 177	418 ± 192
III (5X) puppies	234 ± 27	85 ± 0	98 ± 82	201 ± 69	178 ± 51	167 ± 98	191 ± 0
III (5X) adults	445 ± 141	497 ± 122	379 ± 207	452 ± 175	435 ± 159	322 ± 236	437 ± 122

Values calculated from data on p. 26-29 of MRID 46166108.

F. HEMATOLOGY

From p. 12 of MRID 46166108: "The hematology values were within normal limnits except for platelet counts, prothrombin time and/or activated partial thromboplastin time. These values were significantly elevated in all groups, including the placebo group, and therefore were not dose related."

There were no indications of any treatment related effects on hematology parameters. Alkaline phosphatase activity was elevated for puppies in all groups (and was usually above the reference range of 10-150 IU/L), but this is normal for puppies.

G. CLINICAL CHEMISTRY

There were no indications of any treatment related effects on clinical chemistry parameters. As indicated on p. 12 of MRID 46166108 clinical chemistry results "were within normal limits in males and females and the few significant differences among male or female means in any group or between group means did not appear to be related to treatment with the test substance."

H. NECROPSY FINDINGS

As there were no mortalities, there were no necropsy findings.

IV. DISCUSSION

Possible effects related to exposure to the test material included ocular discharge (seen in both eyes of one puppy in Group II at 4-hours post-dosing; classified as very slight; seen in 3 puppies and one adult in Group III in the period from one hour to eight hours following the first dose. In all 3 puppies ocular discharge, when it occurred during this period, was described as very slight. In the adult there was progression to a red, irritated, watery left eye at 8 hours following the first dosage. In addition, very slight to moderate salivation was noted in five dogs (including two puppies) of Group III in the one to eight hours following treatment. Salivation was seen in one adult (#3080, a 32.2-kg male receiving three 1.5-mL doses at each application) at the one hour observation (i.e., presumably one hour after the first treatment), and very slight salivation was seen in this one dog at 3 and 4 hours [following the first dosage], and then moderate salivation was seen at 8 hours. However, no effects ["No Observable Abnormalities"] were then seen in this dog for the remainder of the 14-day observation period.

Adult dogs dosed at the 5X level tended to show a slight mean weight loss in the week following treatment, although there was no indication of an effect on food consumption.

There was no indication of an effect on body weight in puppies at the 1X and 5X dose levels [actually 1.5X and 7.5X dose levels], although their mean food consumption levels for days 0 and 1 were noticeably lower than concurrent values of their controls as well as their own pre-exposure food consumption.

While the Guidelines for this type of study state that the targeted adequate margin of safety is 5X, it is also stated that: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)." The test material was not tested at 3X and effects were noted at 5X. However, the effects noted at 5X, including ocular discharge (also noted in one puppy dosed at what was essentially 1.5X) and salivation were minimal (most occurrences of both ocular discharge and salivation were described as "very slight.") and reasonably transient. It is noteworthy that no systemic neurological signs (such as tremors or ataxia) were observed, and the salivation may have been due to ingestion of small amounts of test material from licking or biting the application area. In addition, the performing laboratory has demonstrated in the past extremely meticulous reporting of observational data in companion animal safety studies, and it is quite likely that these observations would not have been reported from some of the other laboratories which conduct this type of study.

For local dermal effects, one Group III puppy (treated at what was essentially a 7.5X dose level) showed subsequent shoulder lesions (from day 5 through 15) and was noted to scratch this area frequently. Dermal exposure to pyrethroids can cause a burning and/or itching sensation at the application site, and this has to be considered an effect (unless the registrant can provide additional information demonstrating otherwise). However, this was an isolated case, and the three adult dogs treated with 3 unit doses/application with a total of 5 applications (for a total of fifteen 1.5-mL ampules in all) did not show a similar response.

However, one area of concern is that the 1.5 mL ampules (the only size tested in this study) delivered only an average of only 1.17 mL of test material, and the registrant is

proposing packaging this product in 3.0 and 4.5 mL (as well as 1.0 and 1.5 mL) tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2 x 1.17) mL and the 4.5 mL tubes deliver no more than 3.51 (3 x 1.17) mL.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for puppies (12 weeks and older) and adult dogs. **It is concluded then that there is an adequate margin of safety (at least 5X) between the exposure associated with the proposed use level for this formulation** in dogs **and the dose at which significant adverse systemic toxicological effects (not seen in this study, but which might include ear twitching, muscle tremors, drooling) may occur.** For dermal effects an effect was observed in one puppy in Group III (treated at essentially a 7.5X dose level), but in none of the other dogs in this study (including the puppies in Group II), indicating a reasonably low potential for this effect in dogs treated at the proposed use level.

STUDY DEFICIENCIES: The test material was not tested at 3X and effects were noted at 5X. However, the effects noted at 5X, including ocular discharge (also noted in one puppy dosed at what was essentially 1.5X) and salivation were minimal (most occurrences of both ocular discharge and salivation were described as "very slight."). In addition, the performing laboratory has demonstrated in the past extremely good reporting of observational data, and it is quite possible that what was reported in this study would not have been reported from some of the other laboratories which conduct this type of study.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D305953
2. **PC CODES:** 129013 Cyphenothrin, 129032 Pyriproxyfen, 105401 Methoprene
3. **CURRENT DATE:** November 23, 2004
4. **TEST MATERIAL:** Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen). For this action, the test material is being used to support the registration of a product containing 40% Cyphenothrin as sole active ingredient.

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Product Safety Labs (New Jersey)/Project No. 13320/20-MAY-2003	46166103	LD_{50}>2000 mg/kg. Up and down method defaulting to acute tox class method. 2/5 Sprague-Dawley derived female rats died within 24 hrs after dosage at 2000 mg/kg; two rats which survived showed reduced fecal volume, ventral staining and hypoactivity, with recovery by day 4. All survivors gained weight in the period from day 0 to 7 and again from day 7 to 14. Postmortem necropsy of rats which died showed discoloration of the lungs and intestines and fluid-filled stomachs. Findings from rats which survived to terminal sacrifice were unremarkable.	III	A
Acute dermal toxicity/rat/ Product Safety Labs (New Jersey)/Project No. 13321/20-MAY-2003	46166104	LD_{50} > 2000 mg/kg. 5M & 5F Sprague-Dawley derived albino rats were dermally exposed to 2000 mg/kg for 24 hrs; no mortality, no signs of systemic toxicity. Three males had some dermal irritation with clearing by Day 2. All rats gained wt from day 0 to 7 and from day 7 to 14. No gross abnormalities were observed at post-sacrifice necropsy.	III	A
Primary eye irritation/rabbit/ Product Safety Labs (New Jersey)/Project No. 13322/20-MAY-2003	46166105	No corneal opacity. 3/3 rabbit eyes were positive (grade 2) for conjunctival irritation at 1 and 24 hrs. All eyes clear (all scores zero) by 72 hrs.	III	A
Primary dermal irritation/rabbit/ Product Safety Labs (New Jersey)/Project No. 13323/20-MAY-2003	46166106	No edema (all scores for edema = 0). All 3 sites scored 1 for erythema at 1 hr and 2 at 24, 48 and 72 hrs. One site scored 2 for erythema on day 7 while the other two scored 1. All scores zero on dat 10. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.75	IV	A
Dermal sensitization (Buehler method)/guinea pig/Product Safety Labs (New Jersey	46166107	No indication that test material is a dermal sensitizer.	Not a sensitizer	A

Companion animal/adult dog & 12-wk old puppies/ Stillmeadow TX/Project No. 7650/03/20-OCT-2003	46166108	Three groups of dogs, each containing 9 adults & three 12-week old puppies: Group I (control) was treated with the amount of vehicle at 1X; Group II was treated at 1X (dogs 6.8-15 kg: contents from one 1.5 mL ampule; 15.1-29.5 kg: contents of two 1.5 mL ampules; >29.5 kg: contents of three 1.5 mL ampules. Puppies (<6.8 kg) were treated with contents of one 1.5 mL ampule (1.5X). Group III adults were treated at 5X (with treatments at 1-hr intervals) and Group III pups were treated at 7.5X label dose. Administration was as a spot-on and/or stripe treatment on the back. Possible systemic effects noted following administration were ocular discharge in one Group II puppy at 4 hrs post-dose and in 4 Group III animals (including all 3 puppies). Salivation was also noted in 5 Group III dogs in the period (1-8 hrs) following first administration of test material. Puppies (but not adults) showed of Groups II and III also showed lower mean food consumption on days 0 and 1. One Group III puppy showed shoulder lesions (presumably in the area where test material was applied) from day 5 to the end of the study and was noted to scratch this area frequently. No effects on clinical chemistry or hematology parameters. One concern is that 1.5 mL ampules delivered only 1.17 mL test material; registrant is proposing packaging this product in 3.0 & 4.5 mL tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2x1.17)mL and the 4.5 mL tubes deliver no more than 3.51 (3x1.17)mL.	N/A	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated

DP #: (317320)

Decision #: 338118

DATA PACKAGE BEAN SHEET

Date: 24-May-2005

* * * Registration Information * * *

Registration: 2517-IN - SERGEANT'S CYPHENOTHRIN + IGR SQUEEZE-ON FOR DOGS

Company: 2517 - SERGEANT'S PET CARE PRODUCTS, INC.

Risk Manager: RM 13 - George Larocca - (703) 305-6100 Room# CM-2 206

Risk Manager Reviewer: George Larocca GLAROCCA

Sent Date: 23-Jun-2004 Calculated Due Date: 13-Feb-2007 Edited Due Date:

Type of Registration: Product Registration - Section 3

Action Desc: (R26.4) NEW USE;NON-FOOD;INDOOR;

Ingredients: 129032, Pyriproxyfen(2%)

129013, Cyphenothrin(40%)

* * * Data Package Information * * *

Expedite: ◯ Yes ● No Date Sent: 24-May-2005 Due Back:

DP Ingredient: 129013, Cyphenothrin

129032, Pyriproxyfen

DP Title:

CSF Included: ◯ Yes ● No Label Included: ◯ Yes ● No Parent DP #:

	Assigned To	Date In	Date Out	
Organization:	RD / TRB			Last Possible Science Due Date: 13-May-2006
Team Name:	TOX			Science Due Date:
Reviewer Name:	Backus, Byron			Sub-Data Package Due Date:
Contractor Name:				

* * * Studies Sent for Review * * *

* * * Additional Data Package for this Decision * * *

* * * Data Package Instructions * * *

Byron - You completed review of the companion animal safety study for 2517-IN, IL on Nov. 30th and Nov 24th, 2004. Mark Suarez completed review of efficacy data(MRID 46166109) associated with these two products and noted symptoms reported in all dogs in Test Group 2(see attached excerpt). This appears to be inconsistent with what you reported. Mark has electronically sent you a copy of the efficacy study for further consideration.

Re: 2517-AL, IN

COMPANION ANIMAL MRID 461661-08
(Done by STILLMEADOW, INC.)

PLRS
Professional Laboratory and Research Services, Inc.

PLRS 0307
SERGEANT'S CYPHENOTHRIN SPOT-ON

noted on test days 19-38. Dog ID 1ACD1 had red irritated skin on the stomach noted on test days 36-48.

These three dogs in Test Group 1 were treated for the hair loss and/or irritated skin. Dog ID 1ABE1 was treated beginning on test day 8 with nitrofurazone ointment (Lot No. XN0272A, expiration date 11/04) twice daily for seven days and with 1 cc injectable dexamethasone (Lot No. 2090982, expiration date 09/04) once daily for three days. Dog ID 36491 was likewise treated with the same medications for the same duration beginning on test day 22. However, a deviation occurred when on the first day of the seven day treatment the nitrofurazone ointment was administered only once instead of twice. Dog ID 1ACD1 was treated beginning on test day 42 with 1 cc injectable dexamethasone (Lot No. 2090982, expiration date 11/04) once daily for three days and with Gentocin spray (Lot No. 018046, expiration date 06/04) twice daily for seven days.

TREATED w/ 40.9% Cyphenothrin (100 mg/kg body weight) (≤ Label Rate)

Test Group 2 (cyphenothrin): In general, all six dogs in this group responded to treatment with similar reactions. Dog 35022 vomiting was noted on test day 1, head shaking was noted on test days 2, 3 and 5, licking of paws was noted on test days 2-6, rubbing of the head and body on test day 3 and slight tremors all over body on test day 5. Dog ID CNJAZF had slight tremors noted on test day 1, had shaking on test days 1- 5, squinting on test day 1, licking of paws on test days 1-3, unsteadiness on test day 1, circling on test day 2, pacing on test day 4 and rubbing of head on test day 1. Dog ID 36737 had ear twitching noted on test days 1-3, head shaking on test days 1 and 3, licking of paws on test days 1and 5, pacing on test days 4 and 5, and slight body tremors on test days 2 and 3. Dog ID 28625 had head shaking noted on test days 1-3, 5, 7 and 8, ear twitching on test day 3, licking of the paws and genitalia on test days 3 and 4 and hair loss and irritated skin on the right shoulder onto the mid-back on test days 22-47. Dog ID 34911 vomited on test day 1, head shaking was noted on test days 1-4, 7 and 8, licking of genitalia/paws on test days 1-7, hair loss/redness at ear tips on test days 2-5 and 7-33. Dog ID HHCAVJ had head shaking and slight body tremors noted on test day 3.

Post-treatment Flea and Tick Counts and Product Efficacy (Tables 3-25)

TEST DAY 1 (HAND COUNTS)

The mean number of live fleas counted on the dogs in Test Group 1 (Untreated Controls) was 33.2 fleas/dog (range 27 to 45 fleas) and the mean number of live ticks counted on these dogs was 20.0 ticks/dog (range 12 to 31 ticks), Table 3.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: November 24, 2004

MEMORANDUM

Subject: EPA File Symbol: 2517-IN SERGEANT'S CYPHENOTHRIN + IGR SQUEEZE-ON FOR DOGS
DP Barcode: D305948
Decision No.: 338118
PC Codes: 129013 Cyphenothrin (CAS #39515-40-7), 129032 Pyriproxyfen (CAS #95737-68-1)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

To: Linda DeLuise/George LaRocca RM 13
Insecticide Branch
Registration Division (7505C)

Applicant: SERGEANT'S PET CARE PRODUCTS, INC.

FORMULATION DECLARATION FROM LABEL:

Active Ingredient(s):	% by wt
Cyphenothrin (CAS #39515-40-7)	40.0%
Nylar (CAS #95737-68-1)	2.0%
Inert Ingredients:	58.0%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

Tox waiver request for acute inhalation; review of 5 other acute studies and a companion animal study.

BACKGROUND:

This package includes an acute oral LD_{50} study (rat, up-and-down procedure, defaulting to an acute toxic class procedure, MRID 46166103); acute dermal LD_{50} study (rat; MRID 46166104); primary eye irritation study (rabbit; MRID 46166105); primary dermal irritation study (rabbit; 46166106) and a dermal sensitization study (guinea pig; 46166107), as well as a companion animal safety study in dogs (MRID 46166108). The five acute toxicity studies were conducted at Product Safety Labs, New Jersey. The companion animal safety study was conducted at Stillmeadow, Inc. In addition, there is a waiver request for an inhalation study. All studies were conducted on Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL, containing 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar.

RECOMMENDATIONS:

1. The companion animal (dog) safety study in MRID 46166108 has been reviewed and has been classified as acceptable for puppies (12 weeks and older) and adult dogs. It is concluded that there is an adequate margin of safety (at least 5X) between the exposure associated with the proposed use level for this formulation in dogs, and that at which significant adverse systemic effects (not seen in this study, but which might include ear twitching, muscle tremors, drooling) may occur. For dermal effects an effect was observed in one puppy in Group III (treated at essentially a 7.5X dose level), but in none of the other dogs (including the puppies in Group II, dosed at 1.5X) indicating a reasonably low potential for this effect in dogs treated at the proposed use level.

2. It is noted that the test material was supplied in (and applied from) unidose 1.5 mL ampules. However, the report states that the mean volume delivered from a single 1.5 mL ampule was 1.17 mL, and the registrant is proposing packaging this product in 3.0 and 4.5 (as well as 1.0 and 1.5) mL tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2 x 1.17) mL and the 4.5 mL tubes deliver no more than 3.51 (3 x 1.17) mL.

3. The five acute toxicity studies have been reviewed and classified as acceptable. In addition, TRB has no objection to the registrant's waiver request for an acute inhalation study, based on the product form (a yellow liquid), its proposed packaging

(1.0, 1.5, 3.0 or 4.5 mL tubes or ampules), the method of application (as a spot-on or stripe-on to the dog's back), and the relatively low inhalation toxicity of technical Cyphenothrin (one report from the open literature gives a rat LC50 of 1.85 mg/L, or EPA toxicity category III; extrapolating from this the inhalation LC50 value for a 40% Cyphenothrin-60% inert product would then be greater than 4 mg/L, or EPA toxicity category IV by this exposure route).

4. Based on the results of the acute toxicity studies, the following is the acute toxicity profile for EPA File Symbol: 2517-IN SERGEANT'S CYPHENOTHRIN + IGR SQUEEZE-ON FOR DOGS. The signal word of the product would be CAUTION, as proposed by the registrant:

Study Type	Tox. Cat.	Classification & MRID #
Acute Oral LD_{50} (rat)	III	Acceptable (#46166103)
Acute Dermal LD_{50} (rat)	III	Acceptable (#46166104)
Acute Inhalation LC_{50}	IV	Waived
Primary Eye Irritation (rabbit)	III	Acceptable (#46166105)
Primary Dermal Irritation (rabbit)	IV	Acceptable (#46166106)
Dermal Sensitization (guinea pig)	Negative	Acceptable (#46166107)

5. Based on the acute toxicity profile and proposed uses, the following is the precautionary labeling for this product, as obtained from the Label Review System:

PRODUCT ID #: **002517-00080**

PRODUCT NAME: **SERGEANT'S CYPHENOTHRIN + IGR SQUEEZE-ON FOR DOGS**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Harmful if swallowed or absorbed through skin.. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling.

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical advice.

Reviewer: Byron T. Backus, Ph.D. Date: November 19, 2004
Risk Manager (EPA): 13

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs (although this product does not contain Methoprene) with a label declaration of: Cyphenothrin 40.0% and Pyriproxyfen (Nylar) 2.0%.

CITATION: Moore, G. (2003) Acute Oral Toxicity Up and Down Procedure in Rats: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13320, P320/UDP. Unpublished study prepared by Product Safety Labs, Food Product Laboratory and Silliker Laboratories of New Jersey, Inc. 16 p. Study Completion Date: May 20, 2003. MRID 46166103.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46166103), conducted using the up-and-down procedure but defaulting to the acute toxic class method, Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Gokilaht (Cyphenothrin), 3.0% Methoprene and 2.00% Nylar was administered by oral gavage at 2000 mg/kg to a single Sprague-Dawley derived 9-week-old albino fasted (overnight) female rat. When this rat survived, four additional fasted (overnight) female rats of the same strain, age, body weight range (164-182 g) and source (Ace Animals, Inc., Boyertown, PA) were also dosed at 2000 mg/kg.

On the day of dosage rats were observed for several hours for mortality and signs of gross toxicity for several hours post-dosing. They were then observed at least once a day for the remainder of the 14-day observation period.

On the day of dosage rats were observed at least 3 times within the first 4 hours after dosing for clinical signs of toxicity and mortality and then at least once daily for the remainder of the 14-day observation period. Individual body weights were recorded just prior to dosing (Day 0) and on days 7 and 14. Individual body weights were recorded predosing and on days 7 and 14.

Two rats died within 24 hours of dosage with no clinical signs observed prior to death. Two rats which survived showed reduced fecal volume, ventral staining and hypoactivity, with recovery by Day 4. All survivors gained weight in the period from Day 0 (predose) to Day 7 and again from Day 7 to 14.

Postmortem necropsy findings in the rats which died showed discoloration of the lungs and intestines and fluid filled stomachs. Gross necropsy findings in rats surviving to terminal sacrifice were unremarkable.

Estimated Oral LD_{50} in female rats > 2000 mg/kg.

EPA File Symbol 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 40% Cyphenothrin and 2% Pyriproxyfen (Nylar) is in EPA toxicity category III in terms of oral exposure based on the observed LD_{50} (>2000 mg/kg) in female rats.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 16), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Friday, October 15, 2004, 4:37:11 PM
Data file name: Cyphenothrin-IGR.dat
Last modified: 10/15/2004 4:37:11 PM

Test/Substance: Cyphenothrin-IGR
Test type: Limit Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	8040	2000	O	O
2	8198	2000	O	O
3	8239	2000	O	O
4	8372	2000	X	X
5	9407	2000	X	X

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
2000	3	2	5
All Doses	3	2	5

Statistical Estimates:

The LD50 is greater than 2000 mg/kg.

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	-	2/5	-

Statistics - Not necessary to compute the oral LD_{50}.

A. Mortality - As noted in the table above.

B. Ctinical observations - Two rats died within 24 hours of dosage with no clinical signs observed prior to death. Two rats which survived showed reduced fecal volume, ventral staining and hypoactivity, with recovery by Day 4. All survivors gained weight in the period from Day 0 (predose) to Day 7 and again from Day 7 to 14.

C. Gross Necropsy - Postmortem necropsy findings in the rats which died showed discoloration of the lungs and intestines and fluid filled stomachs. Gross necropsy findings in rats surviving to terminal sacrifice were unremarkable.

D. Reviewer's Conclusions: The study is acceptable. EPA File Symbol 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 40% Cyphenothrin and 2% Pyriproxyfen (Nylar) is in EPA toxicity category III in terms of oral toxicity based on the observed LD_{50} (>2000 mg/kg) in female rats.

E. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 22, 2004
Risk Manager (EPA): 13

STUDY TYPE: Acute Dermal Toxicity - Wistar rats - OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs (although this product does not contain Methoprene) with a label declaration of: Cyphenothrin 40.0% and Pyriproxyfen (Nylar) 2.0%.

CITATION: Moore, G. (2003) Acute Dermal Toxicity Study in Rats - Limit Test: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13321, P322. Unpublished study prepared by Product Safety Labs, Food Product Laboratory and Silliker Laboratories of New Jersey, Inc. 16 p. Study Completion Date: May 20, 2003. MRID 46166104.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID #46166104), a group (5M & 5F) of Sprague-Dawley derived albino rats (source: Ace Animals, Inc., Boyertown, PA; Males: 300-318 g; Females: 178-204 g; young adult [indicated by body weight data]) were dermally exposed (approximately 10% of body surface) for 24 hrs to 2000 mg/kg of undiluted Cyphenothrin-IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen). The test material was held in contact by a gauze pad and Durapore tape.

Rats were observed several times after application on day 0 and once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing (day 0) and on days 7 and 14.

There was no mortality and there were no signs of systemic toxicity. Three males showed some dermal irritation (erythema and/or edema) with clearing by day 2. All rats gained weight from day 0 to 7 and from day 7 to 14.

No gross abnormalities were observed at post-sacrifice necropsy.

Dermal LD_{50} Males > 2000 mg/kg (0/5 died)
Females > 2000 mg/kg (0/5 died)
Combined > 2000 mg/kg (0/10 died)

Based on the rat LD_{50} > 2000 mg/kg, Cyphenothrin-IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar is in EPA toxicity category III in terms of dermal toxicity.

This acute dermal study is classified as acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 16), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

Statistics - Not necessary to compute the dermal LD_{50}.

A. **Mortality** - None, as noted in the table above.

B. **Clinical observations** - There were no signs of systemic toxicity. Three males showed some dermal irritation (erythema and/or edema) with clearing by day 2. All rats gained weight from day 0 to 7 and from day 7 to t4.

C. **Gross Necropsy** - No gross abnormalities were observed at post-sacrifice necropsy.

D. **Reviewer's Conclusions:** The study is acceptable. Based on the rat LD_{50} > 2000 mg/kg, Cyphenothrin-IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is in EPA toxicity category III in terms of dermal toxicity.

E. **Deficiencies** - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 23, 2004
Risk Manager (EPA): 13

STUDY TYPE: Primary Eye Irritation - NZW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs (although this product does not contain Methoprene) with a label declaration of Cyphenothrin 40.0% and Pyriproxyfen (Nylar) 2.0%.

CITATION: Moore, G. (2003) Primary Eye Irritation Study in Rabbits: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13322, P324. Unpublished study prepared by Product Safety Labs, Food Products Laboratory and Silliker Laboratories of New Jersey, Inc. 17 p. Study Completion Date: May 20, 2003. MRID 46166105.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46166105), 0.1 mL of undiluted Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen), was instilled into the conjunctival sac of one eye of each of 3 adult New Zealand White Rabbits (weights: not reported; ages: young adult; source: Davidson's Mill Farm, South Brunswick, NJ), with observations and scoring at 1, 24, 48 and 72 hours after instillation.

No corneal opacity was observed (with 2% ophthalmic fluorescein sodium used at 24 hours to verify the absence of corneal opacity at that reading). 3/3 eyes were positive for conjunctival redness (score of 2) at 1 and 24 hours. All eyes were completely clear (all scores zero) at 72 hours.

In this study, Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is in EPA toxicity category III based on the presence of grade 2 conjunctival redness in 3/3 eyes at 24 hrs which subsequently cleared by 72 hrs.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 17), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested			
	1 hr	24 hrs[2]	48 hrs	72 hrs
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness[1]	3/3	3/3	0/3	0/3
Chemosis[1]	0/3	0/3	0/3	0/3
Discharge[1]	3/3	0/3	0/3	0/3

[1]Score of 2 or more considered positive
[2]Fluorescein staining was used to verify the absence of corneal opacity.

A. Observations - No systemic effects were observed. 3/3 eyes were positive for conjunctival redness (score of 2) at 1 and 24 hours. All eyes were completely clear (all scores zero) at 72 hours.

B. Reviewer's Conclusions: The study adequately defines a Toxicity Category III hazard potential in terms of eye exposure potential for Cyphenothrin-IGR Squeeze-On for Dogs, a clear, light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen).

C. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. **Date:** November 23, 2004
Risk Manager (EPA): 13

STUDY TYPE: Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs (although this product does not contain Methoprene) with a label declaration of Cyphenothrin 40.0% and Pyriproxyfen (Nylar) 2.0%.

CITATION: Moore, G. (2003) Primary Skin Irritation Study in Rabbits: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13323, P326. Unpublished study prepared by Product Safety Labs, Food Products Laboratory and Silliker Laboratories of New Jersey, Inc. 17 p. Study Completion Date: May 20, 2003. MRID 46166106.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46166106), 0.5 mL aliquots of undiluted Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen), were applied to dermal sites on each of 3 (2M & 1F) young adult New Zealand White albino rabbits (source: Davidson's Mill Farm, South Brunswick, NJ) with 4-hour semioccluded exposure.

After 4 hours, the gauze patch and holding tape were removed. The test sites were scored (Draize) at 1, 24, 48 and 72 hrs and at 7 and 10 days.

No edema was observed (all scores for edema were zero). All sites scored one for erythema at 1 hour and 2 at 24, 48 and 72 hours. One site scored 2 for erythema on day 7 while the other two scored 1. All scores were zero on day 10. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.75.

In this study, Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is in EPA Toxicity Category IV for dermal irritation effects, based on the PII of 1.75 and relatively low score (grade 2, characterized as well-defined) for erythema at 72 hrs [EPA Toxicity Category III would be characterized by moderate or grade 3 erythema at 72 hrs) following 4-hr semi-occluded exposure.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 17), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

A. Observations - No edema was observed (all scores for edema were zero). All sites scored one for erythema at 1 hour and 2 at 24, 48 and 72 hours. One site scored 2 for erythema on day 7 while the other two scored 1. All scores were zero on day 10. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.75.

B. Results - The PII (average of 1, 24, 48 and 72-hour scores) = 1.75 The mean irritation score on day 3 was 2.0 (erythema: 2.0; edema: 0.0).

C. Reviewer's Conclusions - The study adequately demonstrates a Toxicity Category IV hazard potential in terms of dermal irritation for Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen).

D. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D. Date: November 23, 2004
Product Manager (EPA): 13

STUDY TYPE: Dermal Sensitization - albino Guinea Pig; OPPTS 870.2600; OECD 406, 429

TEST MATERIAL (% a.i.): Cyphenothrin-IGR Squeeze-On for Dogs (2824) MGK GLP Project #1683A - Lab Prepared. From the certificate of analysis (p. 15 of MRID 4666103) this contained 39.87% Gokilaht (Cyphenothrin), 3.00% Methoprene and 2.00% Nylar. From information on p. 11 of MRID 46166104 the specific gravity of the test material was 1.061 g/mL. The test material is described as a clear, light yellow liquid.

SYNONYMS: The test material description is consistent with the proposed product 2517-IN Sergeant's Cyphenothrin + IGR Squeeze-On for Dogs (although this product does not contain Methoprene) with a label declaration of Cyphenothrin 40.0% and Pyriproxyfen (Nylar) 2.0%.

CITATION: Moore, G. (2003) Dermal Sensitization Study in Guinea Pigs: Buehler Method: Cyphenothrin-IGR Squeeze-On for Dogs. Project Number: 13324, P328. Unpublished study prepared by Product Safety Labs, Food Products Laboratory and Silliker Laboratories of New Jersey, Inc. 25 p. Study Completion Date: May 20, 2003. MRID 46166107.

SPONSOR: MCLAUGHLIN GORMLEY KING COMPANY, 8810 Tenth Avenue North, Minneapolis, MN 55427

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46166107) with Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen), a group of 20M Hartley albino guinea pigs (373-428 g; young adult; source: Elm Hill Breeding Labs, Chelmsford, MA) were each dermally exposed (6 hours) to a 0.4 mL aliquot of test material on a once-a-week basis for 3 consecutive weeks. After a two week rest period they were then dermally challenged with 0.4 mL of a 75% w/w mixture of the test material in mineral oil at a previously unexposed site. An additional 10 previously unexposed male guinea pigs received were similarly treated. Challenge sites on all 30 guinea pigs were evaluated and scored for erythema at 24 and 48 hours after the application.

Following challenge, 7/20 previously exposed guinea pigs showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours. 4/10 controls showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours.

The report includes results from a positive control study (PSL Study #12371) which was conducted with technical (85%) alpha-Hexylcinnamaldehyde and completed on August 15, 2002. The results (3/10 previously exposed, 0/5 naive control guinea pigs showing a positive response at challenge) were appropriate. The study dates for the testing with Cyphenothrin-IGR Squeeze-On for Dogs were from March 13 to April 11, 2003. While slightly outside the 6-month period indicated in the Guidelines, it is concluded the overall study findings are acceptable.

In this study **there were no indications that Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is a dermal sensitizer.**

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406, 429) in the Guinea pig.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 25), and [No] Data Confidentiality (p. 2) statements were provided.

I. PROCEDURE

A. Induction - Each of 20 male Hartley albino guinea pigs was treated once a week for 3 consecutive weeks to a 6-hour exposure to 0.4 mL undiluted Cyphenothrin-IGR Squeeze-On for Dogs.

B. Challenge - Twenty-seven days after the first induction exposure 0.4 mL of a 75% w/w mixture of the test material in mineral oil was applied to a naive site on the right side of each guinea pig at a previously unexposed site. These sites were evaluated and scored for erythema at 24 and 48 hours after the challenge application.

C. Naive Controls - At the time the 20 previously induced guinea pigs were challenged, 10 previously unexposed (negative control) guinea pigs were similarly challenged.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Following challenge, 7/20 previously exposed guinea pigs showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours. 4/10 controls showed very slight (score of 0.5) erythema at 24 hours; all scored zero at 48 hours.

B. Positive control - The report includes results from a positive control study (PSL Study #12371) which was conducted with technical (85%) alpha-Hexylcinnamaldehyde and completed on August 15, 2002. The results (3/10 previously exposed, 0/5 naive control guinea pigs showing a positive response at challenge) were appropriate. The study dates for the testing with Cyphenothrin-IGR Squeeze-On for Dogs were from March 13 to April 11, 2003. While slightly outside the 6-month period indicated in the Guidelines, it is concluded the overall study findings are acceptable.

C. Reviewer's Conclusions: Based on the results of this study **Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen) is not a dermal sensitizer.**

D. Deficiencies - The final date for the cited positive control study is approximately 7 months before the initiation of this study. However, TRB can accept the results of this study.

EPA Primary Reviewer: Byron T. Backus, Ph.D. Signature: _____
Technical Review Branch, Registration Division (7505C) Date_____
EPA Secondary Reviewer: William Dykstra, Ph.D. Signature: _____
Health Effects Division (7509C) Date_____

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety - Dogs OPPTS 870.7200

PC CODES: 129013 (Cyphenothrin), 129032 **DP BARCODE:** D305948
RISK MANAGER: (EPA): 13 **DECISION NO.:**338118

PRODUCT AND TEST MATERIAL: Cyphenothrin-IGR Spot-on for Dogs. [EPA File Symbol 2517-IN]; a liquid labeled "Gokilaht Spot-On w/IGR's (2824) 40.00% RS-Gokilaht; 3.00% S-Methoprene; 2.00% Nylar." According to a certificate of analysis (p. 47 of MRID 46166108) the formulation contained 39.87% Gokilaht, 3.00% S-Methoprene and 2.00% Nylar. Packaged in unidose ampules containing 1.5 mL product.

CITATION: Kuhn, J. (2003) Companion Animal Safety Study in Dogs: Cyphenothrin-IGR Spot-on for Dogs. Final Report. Project Number 7650/03. Unpublished study prepared by Stillmeadow, Inc. and Miller, Thomas A. 53 p. Study Completion Date: 20 October 2003. MRID 46166108.

SPONSOR: Sergeant's Pet Care Products, Inc. Omaha, NE 68130-1703.

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 46166108), groups of 12 dogs (from 5 to 9 males in each group) with each group including three 12-week old puppies weighing 4.1-6.1 kg, 2 or 3 dogs weighing 6.8-15 kg, 3 or 4 dogs weighing 15.1-29.5 kg, and 3 weighing >29.5 kg) were dosed with: 1) the amount of vehicle contained in a single dose (Group I, controls); 2) at 1X the label use directions (except for puppies, which were dosed at 1.5X) in Group II, and 3) at 5X the label use directions (except for puppies, which were dosed at 7.5X) in Group III. Group III dogs were treated five times with one hour between each treatment.

The test material was supplied in unidose 1.5 mL ampules. However, the report states that the mean volume delivered from one of these ampules was 1.17 mL. One dose for puppies consisted of material from a single 1.5 mL ampule (the proposed label states that dogs weighing less than 15 lbs [= 6.8 kg] are to be treated with 1.0 mL), for dogs weighing 15-33 lbs (6.8-15 kg) it was 1.5 mL, for dogs weighing 15.1-29.5 kg it was the contents of two 1.5 mL ampules (the proposed label says two 1.5 mL or one 3.0 mL ampule), and for dogs weighing >29.5 kg it was three 1.5 mL ampules (the proposed label says three 1.5 mL or one 4.5 mL ampules). The control material was supplied in bulk and placebo controls were treated with this formulation (without actives) at the rate of 55.13% of the active product dose volumes.

Administration was according to the proposed label directions and involved application of the test substance (or control vehicle) to the skin in a line along the spine starting at the back of the neck. Label directions specify application of the product as a spot-on or stripe treatment between the shoulder blades to dogs weighing up to 15 kgs. For dogs weighing between 15 and 29.5 kg application would be as a spot-on or stripe treatment at two sites on the back, one

between the shoulder blade and one directly in front of the base of the tail. For >29.5 kg the contents of one 1.5 mL ampule would be applied to the back as a spot-on or stripe between the shoulder, and the contents of the other two 1.5 mL ampules would be applied as a stripe on the back in front of the base of the tail.

Each dog in Groups I and II was observed at 1, 2, 3 and 4 hours following treatment on Day 0. Group III dogs were also observed "between the hourly dosings" (1, 2, 3, 4, 5, 6, 7 and 8 hours after the first treatment). All dogs were then observed twice (a.m. and p.m.) on Days 1-15.

Individual body weights were determined on Days -7, -3, 7 and 14. Individual food consumption was determined on a daily basis from Day -7 through Day 15 by measuring the amount of food given to each dog in the morning and subtracting the amount left at the end of the day. Blood samples were taken on Days -7 and 1 following overnight fasts.

Possible systemic effects related to exposure to the test material included ocular discharge and salivation. In the immediate period following treatment, ocular discharge was observed in one Group II dog (a puppy) at 4 hours post-dose, and in 4 Group III dogs (including all three puppies). Salivation (mostly very slight, but in some cases moderate) was observed in five Group III dogs (including 1/3 puppies), and was observed (very slight) in one adult 32.2 kg dog at 1 hour postdose (so at this time this dog had presumably been treated with only 1 or 2 applications of test material). Salivation was seen in another Group III adult starting at 3 hours, and in two additional Group III adults starting at 4 hours. During the subsequent 15-day observation period, ocular discharge was frequently observed (including continuously from day 10 to 15) in one control puppy, in none of the Group II (1X) dogs, and in one Group III puppy (days 1-2) and one Group III adult (days 1-6, then again on Days 13-15); both of these Group III animals had also shown ocular discharge in the period immediately following the first treatment. Salivation was observed in one Group III adult male at the AM observation on Day 1 (this dog had also showed salivation during the 8-hour period following the first treatment). One Group III male puppy showed a lesion (or lesions) on both sides of the shoulder (presumably at or near the application site) from Day 5 through 15, and was observed to scratch this area frequently.

Group III adults showed a mean weight loss between days -3 and +7. The incidences of adult dogs showing weight losses between days -3 and +7 were: Group I: 3/9; Group II: 4/9: Group III: 6/9. It is concluded then that for adult dogs exposure to a 5X dosage of test material was associated with a slight mean weight decrease in the period from Day -3 to Day 7.

While Group I puppies showed a greater mean weight gain in the period from Day -3 to +7 than Groups II and III, their mean weight gain/day in the subsequent period from Day 7 to 14 (0.053 kg/day) was comparable to the mean weight gains from Day -3 to +7 for Groups II (0.033 kg/day) and III (0.047 kg/day). Group III puppies also showed a greater mean weight gain in the period from Day -3 to 7 than did Group II puppies. There is no indication then that exposure to the test material affected body weight gain in puppies.

Puppies in Groups II and III showed lower mean food consumption values on Days 0 and 1 relative to their controls. This has to be considered as treatment-related. A similar effect in the adults was not evident.

No effects were noted on hematological or clinical chemistry parameters.

While the Guidelines for this type of study state that the targeted adequate margin of safety is 5X, it is also stated that: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)." The test material was not tested at 3X and effects were noted at 5X. However, the

effects noted at 5X, including ocular discharge (also noted in one puppy dosed at what was essentially 1.5X) and salivation were minimal (most occurrences of both ocular discharge and salivation were described as "very slight.") and reasonably transient. It is noteworthy that no systemic neurological signs (such as tremors or ataxia) were observed, and the salivation may have been due to ingestion of small amounts of test material from licking or biting the application area. In addition, the performing laboratory has demonstrated in the past extremely meticulous reporting of observational data in companion animal safety studies, and it is quite likely that these observations would not have been reported from some of the other laboratories which conduct this type of study.

For local dermal effects, one puppy treated at what was essentially a 7.5X dose level showed subsequent shoulder lesions and was noted to scratch this area frequently. Dermal exposure to pyrethroids can cause a burning and/or itching sensation at the application site, and this has to be considered an effect (unless the registrant can provide additional information demonstrating otherwise). However, this was an isolated case, and the three adult dogs treated with 3 unit doses/application with a total of 5 applications (for a total of fifteen 1.5-mL ampules in all) did not show a similar response.

However, one area of concern is that the 1.5 mL ampules (the only size tested in this study) delivered only an average of only 1.17 mL of test material, and the registrant is proposing packaging this product in 3.0 and 4.5 mL (as well as 1.0 and 1.5 mL) tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2 x 1.17) mL and the 4.5 mL tubes deliver no more than 3.51 (3 x 1.17) mL.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for puppies (12 weeks and older) and adult dogs. **It is concluded that there is an adequate margin of safety (at least 5X) between the exposure associated with the proposed use level for this formulation in dogs and that at which significant adverse systemic effects (not seen in this study, but which might include ear twitching, muscle tremors, drooling) may occur.** For dermal effects an effect was observed in one puppy in Group III (treated at essentially a 7.5X dose level), but in none of the other dogs (including the puppies in Group II), indicating a reasonably low potential for this effect in dogs treated at the proposed use level.

COMPLIANCE: Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: Cyphenothrin-IGR Spot-on for Dogs, with a label declaration for active ingredients of RS-Gokilaht [=Cyphenothrin] (40.00%) , S-Methoprene (3.00%), and Nylar (2.00%). According to a certificate of analysis on p. 47 of MRID 46166108 the respective analytical values were 39.87%, 3.00% and 2.00%. Packaged in unit dose ampules containing 1.5 mL.
   Description: A liquid;
   Lot No.: #1683B
   Storage: Room Temperature

2. Administration: Topical (spot-on)

3. Vehicle control: X-5699-03 (Placebo Control); From Study 0310: Lot #03390A0100. liquid which was stored at room temperature.

4. Test animals
   Species: Dog
   Breed: From p. 9 of MRID 46166108: "Beagles and other breeds..."
   Ages and weights at study initiation: "Animals were at least 3 months old at dosing. There were 3 animals from each group in each of the following weight ranges: <15, 15-33, 34-65 and >65 pounds (<6.8, 6.8-15, 15.1-29.5 and >29.5 kg). All dogs less than 15 pounds were pups that were 12 weeks old at dosing." [Note by reviewer: The alkaline phosphatase measurments from Dog 2854F (controls), 3085M (Group II) and 2156M (Group III) were relatively high - refer to pp. 32-34 - suggesting these were fairly young dogs too].
   Sources: Butler Farms (Clyde, NY), Martin Creek Kennels (Williford, AR), Ridglan Farms (Mt. Horeb, WI) and STILLMEADOW, Inc.
   Housing: Individually in kennels measuring 3' x 5.5'.
   Diet: PMI Canine High Density Diet 5L18.
   Water: Tap water, *ad libitum*
   Environmental conditions:
      Temperature: 22° ± 3°C
      Humidity: 30 - 70%
      Air changes: 10 - 12/hr
      Photoperiod: 12 hr dark/12 hr light
   Acclimation period: 2 weeks

II. STUDY DESIGN

A. IN LIFE DATES

From the report cover: study initiation date: 13 August 2003; study completion date: 20 October 2003.

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

There were a total of 12 dogs per dosage group. Group 1 (1X vehicle; note: observation schedule on p. 16 of MRID 46166108 is the same for Groups 1 and 2, consistent with a single application of placebo on dogs in Group 1) consisted of 9 males and 3 females; Group II (1X) consisted of 5 males and 7 females, and Group III (5X) consisted of 8 males and 4 females. Assignment was on the basis of weight. From p. 10 of MRID 46166108: "Animals selected for testing were randomly assigned to three groups... Since there were three dose sizes (based on animal body weight) to be used in each treatment group, three dogs of each weight range were included in each group. The weight ranges were <15, 15-33, 34-65 and >65 pounds (<6.6, 6.8-15, 15.1-29.5 and >29.5 kg). The dogs <15 pounds were 3-month old puppies."

From p. 10 of MRID 46166108: "The test substance and placebo were applied to the skin in a line along the spine starting at the back of the neck. The test substance was supplied in unit dose plastic tubes, each containing 1.5 mL and were administered to each animal according to its body weight. The placebo control substance was provided in bulk. On Day 0, a label dose (1X) of the test substance was administered to each Group II animal according to body weight. Group III animals received the test substance at five times the label dose (5X) administered as single doses once every hour for 5 hours. The single dose volumes were: dogs <15 pounds, 1.5 mL (one unit dose); dogs 13 [15?]-33 pounds, 1.5 mL (one unit dose); dogs 34-65 pounds, 3 mL (two unit doses); and dogs >65 pounds, 4.5 mL (three unit doses). Group I was treated with the placebo control material in a volume equivalent to that of the normal label dose of the test substance less the volume of that dose that was occupied by the active ingredients [or approximately

55% of a normal 1X dose volume]..."

TABLE 1. Study design							
Group & Weight Range (kg)		Number of dogs or puppies		Cumulative Dose/dog			Number of applications
		Male	Female	Total/Dog	Mean mL/kg	Mean Dosage Cyphenothrin (mg/kg)[d]	
I (control)	<6.6[a]	3	0	0.83 mL[b]	0.16[b]	0	1
	6.8-15	1	1	0.83 mL[b]	0.08[b]	0	
	15.1-29.5	2	2	1.65 mL[b]	0.09[b]	0	
	>29.5	3	0	2.48 mL[b]	0.07[b]	0	
II (1X)	<6.6[a]	1	2	1.17 mL[c]	0.28[c]	112[d] (121][e]	1
	6.8-15	1	2	1.17 mL[c]	0.09[c]	36[d] [39][e]	
	15.1-29.5	1	2	2.34 mL[c]	0.12[c]	48[d] [52][e]	
	>29.5	2	1	3.51 mL[c]	0.11[c]	42[d] [45][e]	
III (5X)	<6.6[a]	1	2	5.85 mL[c]	1.26[c]	503[d] [543][e]	5
	6.8-15	0	2	5.85 mL[c]	0.51[c]	207[d] [224][e]	
	15.1-29.5	3	1	11.7 mL[c]	0.64[c]	255[d] [275][e]	
	>29.5	3	0	17.55 mL[c]	0.50[c]	199[d] [215][e]	

Data calculated from information on p. 14-15 in MRID 46166108.
[a] Puppies
[b] Placebo
[c] Test material (with actives); amount delivered based on 1.17 mL/application.
[d] Based on a specific gravity for the test material of 1.00 g/mL (consistent with the calculations for dosage as reported on pp. 14-15 of MRID 46166108) and based on 1.17 mL delivered/tube.
[e] Based on a specific gravity of 1.08 g/mL
Note: According to the CSF the specific gravity of the proposed product is about 1.08; assuming the product contains 40% Cyphenothrin then 1.5 mL would be 1.62 g and would contain 648 mg of Cyphenothrin. The calculations of dosage of Cyphenothrin in the report (see p. 14-15 of MRID 46166108) appear to be based on a specific gravity for the proposed product of about 1.00. Example: Dog 3067 F weighing 4.2 kg received one 1.5 mL dose of the product and this is reported as a dosage of 142 mg/kg Cyphenothrin. 142 mg/kg x 4.2 kg = 596.4 mg; dividing this by 0.3987 (the analytical percentage) gives 1496 mg (= 1.496 g) total product applied. However, in Appendix G (see p. 52 of MRID 46166108) it is stated that the unit dose containers did not deliver the entire target dose of 1.5 mL, as there was a mean delivered volume of 1.17 mL. A statement in Appendix G ("...5X dose rates ranged from 494 to 630 mg/kg for the smallest subjects.") is consistent with delivery of 1.17 mL/dose and a specific gravity of about 1.08 g/mL.

C. DOSE SELECTION RATIONALE

According to the proposed label this product will be packaged in unidose 1.0, 1.5, 3.0 and 4.5 mL applicator tubes. These correspond to single treatments for dogs weighing 15 lbs and under, 15-33 lbs, 33-66 lbs and >66 lbs. However, in this study, Group 2 (1X) dogs (puppies) weighing less than 15 lbs received 1.5 mL (instead of 1.0 mL), while Group 3 (5X) dogs (puppies) weighing less than 15 lbs received 5 x 1.5 mL = 7.5 mL (instead of 5 x 1.0 mL = 5.0 mL).

D. EXPERIMENTAL DESIGN

From p. 10 of MRID 46166108: "Each animal was observed at 1, 2, 3 and 4 hours following dosing on Day 0 and then twice daily [AM and PM] for the duration of the study. Group III animals were also observed between the hourly dosings. Each animal was examined for signs of any pharmacologic and/or toxicologic effects. Only abnormalities were recorded."

Individual dogs were weighed on Days -7, -3, 7 and 14.

Individual food consumption was measured daily by measuring the amount of food given to each dog in the morning and subtracting the amount of food left at the end of the day.

Baseline blood samples were collected from each dog on Day -7 by jugular venipuncture following an overnight fast. Blood samples were also similarly collected on Day 1.

E. PATHOLOGICAL PARAMETERS

Blood samples were collected on Study Days -7, and 1 by jugular venipuncture following an overnight fast. The CHECKED (X) parameters were examined:

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin (Alb)*
X	Chloride*	X	Blood creatinine (Crea)*
	Magnesium	X	Blood urea nitrogen (BUN)*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin (Glob)*
X	Sodium*	X	Glucose (Gluc)*
		X	Total and direct bilirubin (T Bil & D Bil)*
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase(ALPor ALK)*		Triglycerides
	Cholinesterase(ChE)		Serum protein electrophoresis
	Creatine kinase	X	Albumin/Globulin (A/G) ratio
	Lactic acid dehydrogenase(LDH)		
X	Serum alanine aminotransferase (ALT or SGPT)*		
X	Serum aspartate aminotransferase(AST or SGOT)*		
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

The statistical report is found in Appendix G. It consists of a 6-page document (pages 48-53 of MRID 46166108). From p. 51 of MRID 46166108: "The data generated by the test facility...were statistically analyzed by Student's "t" test, assuming equal variances, using the statistical program in Microsoft Excel, version 97-SR-1... Since cyphenothrin is potentially the most toxic component of the product (pyriproxyfen and methoprene are known to be virtually mammalian-inert) cyphenothrin dosage was the focus. To ensure that some of the test subjects were treated at or above the target maximum dose rate of 100 mg of cyphenothrin per kg body weight, the 12-week-old Beagle pups were treated with the next higher unit dose volume. Although weighing between 9 and 11 lb at treatment, for which the proposed label dose rate is one dose of 1 mL, these pups received one 1.5 mL unit dose. To validate the dosage delivered to the principals, the expelled contents of six 1.5 mL unit dose containers were each weighed..." [Note: the report text then refers to Table 1.1, which is not present in the report]. From p. 52 of the report: "The dose validation data (Table 1.1) indicated that the unit dose containers, if filled at the target dose volume of 1.5 mL, were not capable of delivering the entire target volume (mean volume delivered was 1.17 mL).

G. DISPOSITION OF ANIMALS

Not stated. According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals."

H. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The dose per 1.17 mL application (based on a product specific gravity of 1.08 g/mL) is 1.264 g. Since the test material contained (by analysis) 39.87% Cyphenothrin, 3.00% S-Methoprene and 2.00% Nylar, each 1.17 mL dose then contained 0.504 g (=504 mg) Cyphenothrin, 0.038 g (=38 mg) S-Methoprene and 0.025 g (=25 mg) Nylar. For Group II (1X) mean cumulative Cyphenothrin dosages were: puppies (<6.6 kg): 121 mg/kg; dogs 6.8-15 kg: 39 mg/kg; dogs 15.1-29.5 kg: 52 mg/kg; and dogs >29.5 kg: 45 mg/kg. For Group III (5X) dosages were: puppies (<6.6 kg): 543 mg/kg; dogs 6.8-15 kg: 224 mg/kg; dogs 15.1-29.5 kg: 255 mg/kg; and dogs >29.5 kg: 215 mg/kg. Refer to Table 1 of this DER. B. MORTALITY

There was no mortality, with all dogs surviving the 14-day observation period.

C. CLINICAL SIGNS

In the observation period immediately following treatment, no clinical signs of systemic toxicity were observed in Group I (controls). In Group II (1X) animal 3074 (a male pup weighing 4.1 kg) showed very slight ocular discharge from both eyes at 4 hours post-dose. In Group III (5X) four dogs (including all 3 puppies) showed very slight to moderate ocular discharge from one or both eyes in the period from one hour to 8 hours post-dosing. In addition, five dogs (including one puppy) showed very slight to moderate salivation during this period (in two dogs it was classified as very slight). Very slight salivation occurred in one animal at 1 hour (i.e., presumably following a single dosage of test material), and in two others it was first noted at 3 hours (after 3 application treatments)

Slight to moderate green ocular discharge (both eyes) was observed in one control puppy in the period from Day 1 to Day 6, and then again in this puppy from Day 10 to Day 15. No ocular discharge was observed in Group II in the period from Day 1 to Day 15. One Group III puppy showed clear ocular discharge from the left eye on Days 1 and 2, while an adult dog showed clear ocular discharge from the left eye from Day 1 through Day 6, then again from Day 13 through Day 15.

TABLE 2. Adverse Effects Observed in Dogs Treated with Cyphenothrin-IGR Spot-on In the Period Immediately Following Treatment[a]

Parameter	Group I (Control)	Group II (1X)	Group III (5X)
Ocular discharge - one or both eyes in the immediate post-dosing period	0[0]	1[1/48]	4[12/96]
Salivation	0[0]	0[0]	5[18/96]
Soft stool	0[0]	0	2[2/96]
Spiked greasy hair at application site in the immediate post-dosing period	0[0]	2[2/48]	0[0[

[a]Data taken from Table 2 (p. 15) of MRID 46166108.

From p. 11 of MRID 46166108: "Five of the Group II [1X] animals exhibited greasy spiked fur and/or white deposits at the dose site through Day 3. The only other observation noted in this group was moderate white foamy vomit in one dog on Day 8. In Group III, greasy and/or spiked fur and/or white deposits were seen through Day 1 in two dogs, through Day 3 in three dogs, through Day 6 in three dogs and [from Day 5] through Day 15 in one dog. Other observations included slight clear ocular discharge through Day 2 and shoulder lesions through Day 15 in one animal (the dog was observed to scratch the irritated area frequently), and slight to moderate diarrhea on Days 3 and 4 in another animal. Another dog had very slight to moderate clear ocular discharge through study termination with slight to moderate redness around the eye on Days 3-6. One dog exhibited slight salivation on Day 1 and moderate diarrhea on Day 14, and another had a lesion on the back on Days 7-15."

The Group III dog with the lesions on the shoulder (from p. 18: "both sides") from Day 5 through 15 was 3070M (a male puppy), treated with five 1.5 mL applications, while the Group III dog with the lesion on the back (Days 7-15) was 2853F (a female adult) also treated with five 1.5 mL applications.

D. BODY WEIGHT AND WEIGHT GAIN

From p. 12 of MRID 46166108: "The average weight gain[s] for Groups I, II and III were 1.1, 1.0 and 0.6 kilograms, respectively. There were no significant differences among groups, and no dose related responses."

The values in Table 3 are calculated from individual body weight data (p. 14-15 of MRID 46166108):

TABLE 3. Mean Body Weights for Dogs by Group

Group	kg ± S.D.				Mean Wt change Day -3 to 7	Mean Wt change Day -3 to 14
	Day -7	Day -3	Day 7	Day 14	kg ± S.D.	kg ± S.D.
I (Controls) puppies	4.63 ± 0.50	5.07 ± 0.93	6.13 ± 1.01	6.50 ± 1.10	1.07 ± 0.15	1.43 ± 0.31
I (Controls) adults	21.87 ± 9.93	22.34 ± 10.26	22.86 ± 10.90	23.31 ± 11.15	0.51 ± 0.87	0.97 ± 1.00
II (1X) puppies	4.80 ± 1.14	4.17 ± 0.06	4.50 ± 0.10	4.97 ± 0.31	0.33 ± 0.15	0.80 ± 0.36
II (1X) adults	21.64 ± 9.61	21.90 ± 9.16	22.53 ± 10.29	22.91 ± 10.29	0.41 ± 1.36	1.01 ± 1.61
III (5X) puppies	4.67 ± 0.71	4.63 ± 0.57	5.10 ± 0.70	5.63 ± 0.50	0.47 ± 0.15	1.00 ± 0.10
III (5X) adults	22.18 ± 10.00	22.38 ± 10.35	22.18 ± 10.40	22.86 ± 10.68	-0.20 ± 0.32	0.48 ± 0.58

Values calculated from data on p. 14 and 15 of MRID 46166108.

The possibility exists that there was a switch of puppies (or their bodyweights) as pup 3073M (assigned to controls) weighed 4.1 kg on day -7 but 6.1 kg on day -3, while pup 3074M (assigned to Group II or 1X) weighed 6.1 kg on day -7 but 4.1 kg on day -3. However, because this switch would have occurred before the dogs were treated, there would have been no impact on the study results.

The only group in which adults showed a mean weight loss between days -3 and +7 was Group III. The incidences of adult dogs showing weight losses between days -3 and +7 were the following: Group I: 3/9; Group II: 4/9: Group III: 6/9. It is concluded then that for adult dogs exposure to a 5X dosage of test material was associated with a slight mean weight decrease in the period from Day -3 to Day 7.

While Group I puppies showed a greater mean weight gain in the period from Day -3 to +7 than Groups II and III, their mean weight gain/day in the subsequent period from Day 7 to 14 (0.053 kg/day) was comparable to the mean weight gains from Day -3 to +7 for Groups II (0.033 kg/day) and III (0.047 kg/day). Group III puppies also showed a greater mean weight gain in the period from Day -3 to 7 than did Group II puppies. There is no indication then that exposure to the test material affected body weight gain in puppies.

TABLE 4. Mean Body Weight Gains for Puppies				
	Day -3 to +7	Day -3	Mean Pup Wt. Gain kg/Day Day -3 to +7	Mean Pup Wt. Gain kg/Day Day 7 to 14
I (Controls) puppies	1.07 ± 0.15	0.37 ± 0.15	0.107	0.053
II (1X) puppies	0.33 ± 0.15	0.47 ± 0.21	0.033	0.067
III (5X) puppies	0.47 ± 0.15	0.53 ± 0.25	0.047	0.076

Values calculated from data on p. 14 and 15 of MRID 46166108.

E. FOOD CONSUMPTION

Puppies in Groups II and III showed lower mean food consumption values on Days 0 and 1 relative to their controls. This has to be considered as treatment-related. A similar effect in the adults was not evident.

TABLE 5. Mean Diet ± S.D. (g) Consumed by Dog/Group by Day							
Group	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
I (Controls) puppies	227 ± 40	267 ± 14	263 ± 17	279 ± 27	315 ± 27	252 ± 41	275 ± 0
I (Controls) adults	431 ± 129	475 ± 131	525 ± 110	496 ± 138	504 ± 166	313 ± 173	496 ± 146
II (1X) puppies	193 ± 7	122 ± 3	89 ± 17	239 ± 45	200 ± 81	165 ± 11	209 ± 15
II (1X) adults	384 ± 218	387 ± 202	339 ± 248	410 ± 207	435 ± 216	310 ± 177	418 ± 192
III (5X) puppies	234 ± 27	85 ± 0	98 ± 82	201 ± 69	178 ± 51	167 ± 98	191 ± 0
III (5X) adults	445 ± 141	497 ± 122	379 ± 207	452 ± 175	435 ± 159	322 ± 236	437 ± 122

Values calculated from data on p. 26-29 of MRID 46166108.

F. HEMATOLOGY

From p. 12 of MRID 46166108: "The hematology values were within normal limnits except for platelet counts, prothrombin time and/or activated partial thromboplastin time. These values were significantly elevated in all groups, including the placebo group, and therefore were not dose related."

There were no indications of any treatment related effects on hematology parameters. Alkaline phosphatase activity was elevated for puppies in all groups (and was usually above the reference range of 10-150 IU/L), but this is normal for puppies.

G. CLINICAL CHEMISTRY

There were no indications of any treatment related effects on clinical chemistry parameters. As indicated on p. 12 of MRID 46166108 clinical chemistry results "were within normal limits in males and females and the few significant differences among male or female means in any group or between group means did not appear to be related to treatment with the test substance."

H. NECROPSY FINDINGS

As there were no mortalities, there were no necropsy findings.

IV. DISCUSSION

Possible effects related to exposure to the test material included ocular discharge (seen in both eyes of one puppy in Group II at 4-hours post-dosing; classified as very slight; seen in 3 puppies and one adult in Group III in the period from one hour to eight hours following the first dose. In all 3 puppies ocular discharge, when it occurred during this period, was described as very slight. In the adult there was progression to a red, irritated, watery left eye at 8 hours following the first dosage. In addition, very slight to moderate salivation was noted in five dogs (including two puppies) of Group III in the one to eight hours following treatment. Salivation was seen in one adult (#3080, a 32.2-kg male receiving three 1.5-mL doses at each application) at the one hour observation (i.e., presumably one hour after the first treatment), and very slight salivation was seen in this one dog at 3 and 4 hours [following the first dosage], and then moderate salivation was seen at 8 hours. However, no effects ["No Observable Abnormalities"] were then seen in this dog for the remainder of the 14-day observation period.

Adult dogs dosed at the 5X level tended to show a slight mean weight loss in the week following treatment, although there was no indication of an effect on food consumption.

There was no indication of an effect on body weight in puppies at the 1X and 5X dose levels [actually 1.5X and 7.5X dose levels[, although their mean food consumption levels for days 0 and 1 were noticeably lower than concurrent values of their controls as well as their own pre-exposure food consumption.

While the Guidelines for this type of study state that the targeted adequate margin of safety is 5X, it is also stated that: "Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)." The test material was not tested at 3X and effects were noted at 5X. However, the effects noted at 5X, including ocular discharge (also noted in one puppy dosed at what was essentially 1.5X) and salivation were minimal (most occurrences of both ocular discharge and salivation were described as "very slight.") and reasonably transient. It is noteworthy that no systemic neurological signs (such as tremors or ataxia) were observed, and the salivation may have been due to ingestion of small amounts of test material from licking or biting the application area. In addition, the performing laboratory has demonstrated in the past extremely meticulous reporting of observational data in companion animal safety studies, and it is quite likely that these observations would not have been reported from some of the other laboratories which conduct this type of study.

For local dermal effects, one Group III puppy (treated at what was essentially a 7.5X dose level) showed subsequent shoulder lesions (from day 5 through 15) and was noted to scratch this area frequently. Dermal exposure to pyrethroids can cause a burning and/or itching sensation at the application site, and this has to be considered an effect (unless the registrant can provide additional information demonstrating otherwise). However, this was an isolated case, and the three adult dogs treated with 3 unit doses/application with a total of 5 applications (for a total of fifteen 1.5-mL ampules in all) did not show a similar response.

However, one area of concern is that the 1.5 mL ampules (the only size tested in this study) delivered only an average of only 1.17 mL of test material, and the registrant is

proposing packaging this product in 3.0 and 4.5 mL (as well as 1.0 and 1.5 mL) tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2 x 1.17) mL and the 4.5 mL tubes deliver no more than 3.51 (3 x 1.17) mL.

This study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) for puppies (12 weeks and older) and adult dogs. **It is concluded then that there is an adequate margin of safety (at least 5X) between the exposure associated with the proposed use level for this formulation in dogs and the dose at which significant adverse systemic toxicological effects (not seen in this study, but which might include ear twitching, muscle tremors, drooling) may occur.** For dermal effects an effect was observed in one puppy in Group III (treated at essentially a 7.5X dose level), but in none of the other dogs in this study (including the puppies in Group II), indicating a reasonably low potential for this effect in dogs treated at the proposed use level.

STUDY DEFICIENCIES: The test material was not tested at 3X and effects were noted at 5X. However, the effects noted at 5X, including ocular discharge (also noted in one puppy dosed at what was essentially 1.5X) and salivation were minimal (most occurrences of both ocular discharge and salivation were described as "very slight."). In addition, the performing laboratory has demonstrated in the past extremely good reporting of observational data, and it is quite possible that what was reported in this study would not have been reported from some of the other laboratories which conduct this type of study.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D305948
2. **PC CODES:** 129013 Cyphenothrin, 129032 Pyriproxyfen, 105401 Methoprene
3. **CURRENT DATE:** November 23, 2004
4. **TEST MATERIAL:** Cyphenothrin-IGR Squeeze-On for Dogs, a clear light yellow liquid with a specific gravity of 1.061 g/mL containing 39.87% Cyphenothrin, 3.00% Methoprene and 2.00% Nylar (Pyriproxyfen)

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Product Safety Labs (New Jersey)/Project No. 13320/20-MAY-2003	46166103	LD_{50}>2000 mg/kg. Up and down method defaulting to acute tox class method. 2/5 Sprague-Dawley derived female rats died within 24 hrs after dosage at 2000 mg/kg; two rats which survived showed reduced fecal volume, ventral staining and hypoactivity, with recovery by day 4. All survivors gained weight in the period from day 0 to 7 and again from day 7 to 14. Postmortem necropsy of rats which died showed discoloration of the lungs and intestines and fluid-filled stomachs. Findings from rats which survived to terminal sacrifice were unremarkable.	III	A
Acute dermal toxicity/rat/ Product Safety Labs (New Jersey)/Project No. 13321/20-MAY-2003	46166104	LD_{50} > 2000 mg/kg. 5M & 5F Sprague-Dawley derived albino rats were dermally exposed to 2000 mg/kg for 24 hrs; no mortality, no signs of systemic toxicity. Three males had some dermal irritation with clearing by Day 2. All rats gained wt from day 0 to 7 and from day 7 to 14. No gross abnormalities were observed at post-sacrifice necropsy.	III	A
Primary eye irritation/rabbit/ Product Safety Labs (New Jersey)/Project No. 13322/20-MAY-2003	46166105	No corneal opacity. 3/3 rabbit eyes were positive (grade 2) for conjunctival irritation at 1 and 24 hrs. All eyes clear (all scores zero) by 72 hrs.	III	A
Primary dermal irritation/rabbit/ Product Safety Labs (New Jersey)/Project No. 13323/20-MAY-2003	46166106	No edema (all scores for edema = 0). All 3 sites scored 1 for erythema at 1 hr and 2 at 24, 48 and 72 hrs. One site scored 2 for erythema on day 7 while the other two scored 1. All scores zero on dat 10. The PII (average of scores at 1, 24, 48 & 72 hrs) = 1.75	IV	A
Dermal sensitization (Buehler method)/guinea pig/Product Safety Labs (New Jersey	46166107	No indication that test material is a dermal sensitizer.	Not a sensitizer	A

Companion animal/adult dog & 12-wk old puppies/ Stillmeadow TX/Project No. 7650/03/20-OCT-2003	46166108	Three groups of dogs, each containing 9 adults & three 12-week old puppies: Group I (control) was treated with the amount of vehicle at 1X; Group II was treated at 1X (dogs 6.8-15 kg: contents from one 1.5 mL ampule; 15.1-29.5 kg: contents of two 1.5 mL ampules; >29.5 kg: contents of three 1.5 mL ampules. Puppies (<6.8 kg) were treated with contents of one 1.5 mL ampule (1.5X). Group III adults were treated at 5X (with treatments at 1-hr intervals) and Group III pups were treated at 7.5X label dose. Administration was as a spot-on and/or stripe treatment on the back. Possible systemic effects noted following administration were ocular discharge in one Group II puppy at 4 hrs post-dose and in 4 Group III animals (including all 3 puppies). Salivation was also noted in 5 Group III dogs in the period (1-8 hrs) following first administration of test material. Puppies (but not adults) showed of Groups II and III also showed lower mean food consumption on days 0 and 1. One Group III puppy showed shoulder lesions (presumably in the area where test material was applied) from day 5 to the end of the study and was noted to scratch this area frequently. No effects on clinical chemistry or hematology parameters. One concern is that 1.5 mL ampules delivered only 1.17 mL test material; registrant is proposing packaging this product in 3.0 & 4.5 mL tubes. This is acceptable only if the 3.0 mL tubes deliver no more than 2.34 (2x1.17)mL and the 4.5 mL tubes deliver no more than 3.51 (3x1.17)mL.	N/A	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated

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June 16, 2004

Document Processing Desk (REGFEE)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Room 266A, Crystal Mall #2
1801 South Bell Street
Arlington, VA 22202

Attn: Mr. George T. LaRocca
Product Manager Team 13

Dear Mr. LaRocca:

RE: Sergeant's Cyphenothrin Squeeze-On For Dogs
EPA Company Number: 2517

This submission for a new registration is being made on behalf of our client, Sergeant's Pet Care Products, Inc. ("Sergeant's"). With this submission, we are utilizing the "Selective Method" of data support and are relying on data developed by Sergeant's as well as data from the McLaughlin Gormley King Company ("MGK Company").

The above referenced proposed product registration contains the active ingredient, Cyphenothrin at 40% a.i. Cyphenothrin is not currently registered for direct application to dogs. However, Cyphenothrin is approved under the General Use-Patterns, "Indoors - Pets", as a fogger, and spray for treatment of pet bedding, pet sleeping quarters, and pet living quarters for control of fleas, ticks, flies and mosquitoes. Such pet treatment uses can be found on approved labeling for the following registrations: EPA Reg. No's 1021-1681, 1021-1684, 1021-1685, 1021-1686, 1021-1765 and 4822-393.

As Cyphenothrin is currently approved under the General Use Pattern of "Indoors - Pets" for treatments made via foggers or spray, we do not believe the use of Cyphenothrin directly on pets ("dogs") would not be meet the definition of a new use as defined in 40 CFR Part 152.3. For this reason we believe the appropriate Fee Category is R31 for the Fee Amount of $4,000.

Included with this request for a new end-use pesticide registration please find the following:

1. EPA Application for Pesticide Registration (EPA Form 8570-1)
2. Transmittal Document/Bibliography of Submitted Data
3. Letter of Consultant Authorization from Sergeant's Pet Care Products, Inc.
4. Letter of Data Support from MGK Company
5. EPA Formulator's Exemption Statement (EPA Form 8570-27)
6. EPA Confidential Statement of Formula (EPA Form 8570-4)
7. Certification of Certified Limits of Ingredients
8. EPA Certification with Respect to Citation of Data (EPA Form 8570-34)
9. EPA Data Matrix (Agency & Public File Copies)(EPA Form 8570-35)
10. Five (5) Copies of Proposed Product Labeling

Three (3) Copies each of the following Data/Studies:

11. Product Properties Data Entitled: *"Product Properties Data (Groups "A") on Sergeant's Cypenothrin Squeeze-On for Dogs"*. OPPTS Test Guidelines: 830.1550, 830.1600, 830.1620, 830.1650, 830.1670, 830.1750 and 830.1800.
12. Product Properties Data Entitled: *"Product Chemistry of Gokilaht Spot-On F-2829"*. OPPTS Test Guidelines: 61-1 to 61-3, 62-1 to 62-3 and 63-2 to 63-21.
13. Acute Inhalation Study Data Waiver Request Entitled: *"Sergeant's Cyphenothrin Squeeze-On for Dogs Waiver Request from the Requirement to Conduct Acute Inhalation Data - 870.1300"*. OPPTS Test Guideline: 870.1300.

We trust you will find everything in order with this submission. Should you have any questions or need additional information please do not hesitate to contact us.

Sincerely,

Marla K. Jackson
Agent for Sergeant's Pet Care Products, Inc.

cc: Mr. Larry Nouvel - Nouvel & Associates, Inc.
Ms. Caryn Stichler - Sergeant's Pet Care Products, Inc.

TRANSMITTAL DOCUMENT
BIBLIOGRAPHY OF SUBMITTED DATA

Submitter: Sergeant's Pet Care Products, Inc.
2637 South 158th Plaza, Ste. 100
Omaha, NE 68130-1703

Product Name: Sergeant's Cypenothrin Squeeze-On for Dogs
"Application for New Product Registration"

EPA Company Number: 2517

Transmittal Date: June 16, 2004

Volume	Data Description	MRID Number
1 of 3	Jackson, M. K. (2004). *"Product Properties Data (Group "A") on Sergeant's Cyphenothrin Squeeze-On for Dogs".* OPPTS Test Guidelines 830.1550, 830.1600, 830.1620, 830.1650, 830.1670, 830.1750 & 830.1800. Unpublished Study by Brazos Associates, Inc.; 1806 Auburn Drive; Carrollton, TX 75007-1451. 6 pages and 6 pages.	46303801
2 of 3	Besser, B. D. (2003). *"Product Chemistry of Gokilaht Spot-On F-2829".* Guideline Numbers 61-1 to 61-3, 62-1 to 62-3, 63-2 to 63-21. Unpublished Study by McLaughlin Gormley King Company; 8810 Tenth Avenue North; Minneapolis, MN 55427. 8 pages.	46303802
3 of 3	Jackson, M. A. (2004). *"Sergeant's Cyphenothrin Squeeze-On For Dogs Waiver Request from the Requirement to Conduct an Acute Inhalation Study-870.1300".* Unpublished Study (Request) by Brazos Associates, Inc.; 1806 Auburn Drive; Carrollton, TX 75007-1451. 6 pages.	Admin.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

June 29, 2004

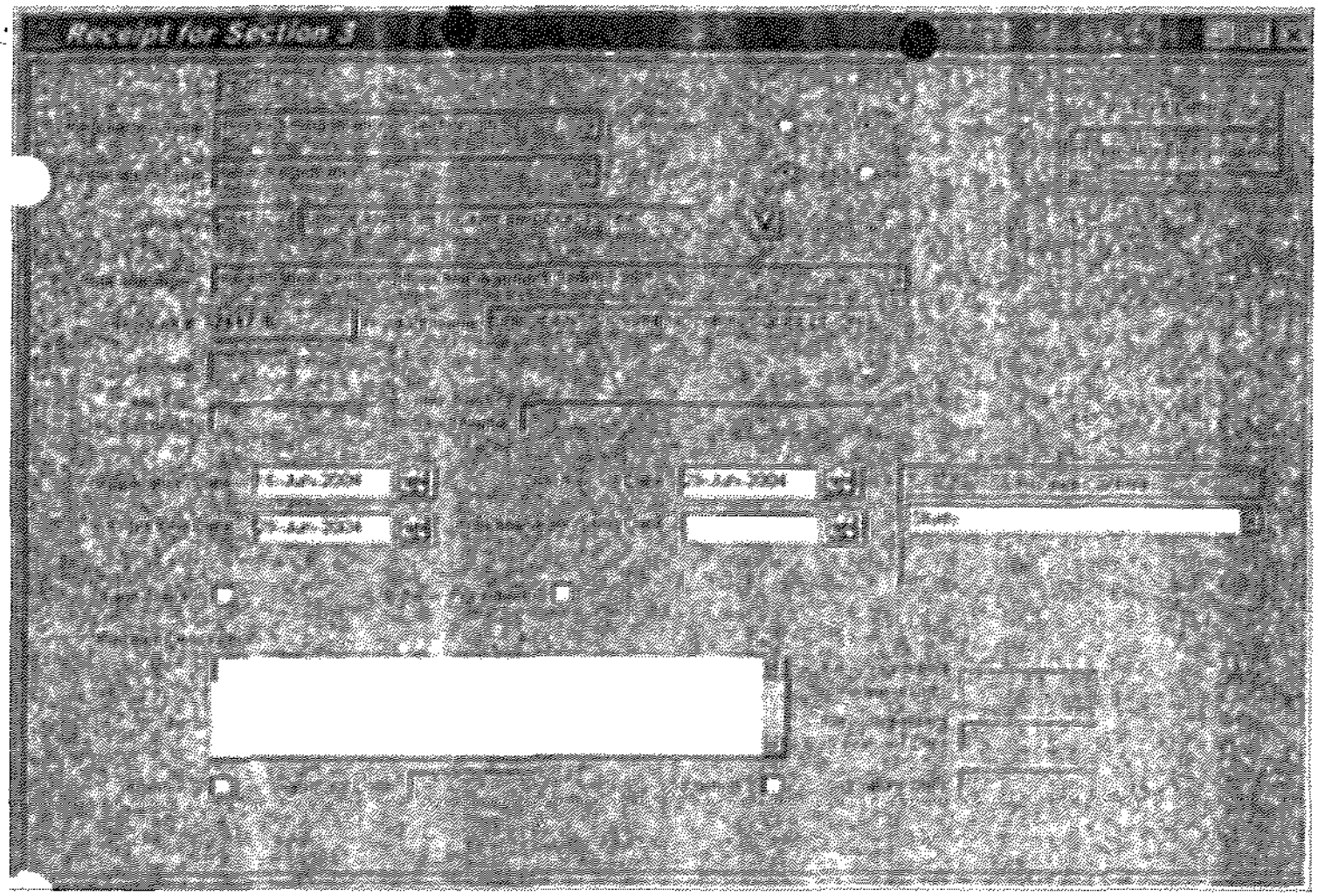
OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SERGEANT'S PET CARE PRODUCTS, INC.
D/B/A SERGEANT'S PET PRODUCTS
1479 WEST POND ROAD
EGAN, MN 55122-

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your submittal of 29-JUN-04. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



Brazos Associates, Inc.®

1806 Auburn Drive • Carrollton, Texas 75007-1451
Phone: 972-939-8390 • Facsimile: 972-939-8370
E-mail: marla@brazosassociates.com

June 16, 2004

Document Processing Desk (REGFEE)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Room 266A, Crystal Mall #2
1801 South Bell Street
Arlington, VA 22202

Attn: Mr. George T. LaRocca
Product Manager Team 13

Dear Mr. LaRocca:

RE: Sergeant's Cyphenothrin Squeeze-On For Dogs
EPA Company Number: 2517

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Sincerely,

Marla K. Jackson
Agent for Sergeant's Pet Care Products, Inc.

cc: Mr. Larry Nouvel - Nouvel & Associates, Inc.
Ms. Caryn Stichler - Sergeant's Pet Care Products, Inc.

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BIBLIOGRAPHY OF SUBMITTED DATA

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2637 South 158th Plaza, Ste. 100
Omaha, NE 68130-1703

Product Name: Sergeant's Cypenothrin Squeeze-On for Dogs
"Application for New Product Registration"

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Exponent

Exponent
1730 Rhode Island Ave., NW
Suite 1100
Washington, DC 20036

telephone 202-772-4900
facsimile 202-772-4979
www.exponent.com

July 19, 2005

George LaRocca
Product Manager 13
Registration Division
U.S. Environmental Protection Agency
Office of Pesticide Programs
Document Processing Desk
1801 South Bell Street
Room 266A, Crystal Mall 2
Arlington, VA 22202

Subject: Meeting Minutes
Project No. WD00758.000

Dear Mr. LaRocca:

On behalf of our client Sergeant's Pet Care Products, Inc. (2637 South 158th Plaza, Suite 100, Omaha, Nebraska 68130-1703, EPA Company Number 2517), Exponent is submitting meeting minutes from our July 13, 2005 meeting with the Agency.

If you have any questions, please contact me at (202) 772-4932.

Sincerely,

James Messina
Authorized Representative of
Sergeant's Pet Care Products, Inc.

Enclosures (1)

cc: Bob Scharf, Sergeant's
Larry Nouvel, Nouvel & Associates

Exponent

Exponent
1730 Rhode Island Ave., NW
Suite 1100
Washington, DC 20036

telephone 202-772-4900
facsimile 202-772-4979
www.exponent.com

Sergeant's/EPA Meeting Minutes
July 13, 2005
10:00 A.M.

Attendees:

Name	Organization	Phone Number
Linda DeLuise	EPA/RD	703-305-5428
Byron T. Backus	TRB/RD	703-305-1968
Margarita Collantes	OPP/HED	703-305-7085
Larry Nouvel	Nouvel Inc./Sergeant's	469-233-2854
Mark Suarez	EPA/RD/IB	703-305-0120
Bob Scharf	Sergeant's	402-938-7000
Jim Messina	Exponent	202-772-4932
Carrie Daniels	Exponent	202-772-4916
Thomas A. Miller	VRRC	360-582-0985
George LaRocca	EPA/RD/IB	703-670-8050

The meeting was opened with introductions and a sign-in sheet was passed around. Bob Scharf gave a general overview of Sergeant's Pet Care and the importance of the pending spot-on products to their business. He further explained the need to obtain registrations as soon as possible, so they can compete in the fall 2005 retail-planning season for Spring 2006 sales. Mr. Scharf also explained that Sergeant's is developing the active ingredient cyphenothrin with the idea of replacing their existing permethrin based product line. The purpose of this is based on the fact that permethrin's risk cup is overflowing and it is anticipated that uses will be affected in the near future.

Cyphenothrin Shampoo Products for Dogs

The first products discussed in detail were the cyphenothrin shampoo products, which Sergeant's is developing. A major question in the product development is what efficacy data is needed to support label claims. The Agency stated that efficacy data and claims must be more than a few hours, specifically more like 1-2 weeks. Sergeant's confirmed that they are seeing residual efficacy of 1-2 weeks and that they are continuing to develop data. Another related question was, on what criteria should they base the mosquito efficacy data? Typically in the past, the Agency wanted to see repellency (or no landings) of mosquitoes. Today the industry, including Sergeant's, is moving towards lack of blood meals in female mosquitoes to confirm that dogs are not being bitten. This is due in part to new product formulations, which are less volatile than previous repellants. Older repellents released more vapor that was effective in preventing landings. New formulations are less volatile and work by preventing feeding. The

Agency agreed that repellency is still used for human products but they will consider lack of blood meals for dogs (pets). The Agency recommended that Sergeant's submit a protocol, preliminary data, and a label for review. Mr. Suarez will review it and discuss it with the Registration Division (RD) and respond to Sergeant's. We asked what the typical review timeframe is for a protocol and the Agency stated that it takes a few weeks to complete.

The efficacy discussion lead to the recently received data evaluation record (DER) for the cyphenothrin companion animal safety study. Dr. Backus discussed the toxicological effects that were observed in one study and the fact that these effects were not observed in any other study. He stated that this must be addressed. Sergeant's stated that some of the effects are not fully explainable. There is one study that effects were observed in; however, there are several other efficacy studies at the same dose level or higher that were submitted to EPA and that did not demonstrate any of these effects. It was agreed that Sergeant's will submit a written response to EPA for review, which will include a discussion of the available data, effects observed by dose level, dose level confirmation, and other supporting information (including references to the studies on file with EPA).

Cyphenothrin Spot-On for Dogs (2517-IN and 2517-IL)

The next issue discussed was the two pending applications under 2517-IN and 2517-IL. The Health Effects Division (HED) is currently working on its risk assessment and plans to complete it in the next few months. Sergeant's asked if there was a more definitive time estimate for completion, as they need to have registrations early this fall to be able to compete in the 2006 use season. This is based on the fact that many retailers start planning their spring inventories during the fall. The EPA stated that they would complete the review and register the products before the end of 2005. They stated that it is possible that they might be registered earlier but that they could not commit to any specific date.

Cyphenothrin + Methoprene Squeeze-On for Dogs

The next product discussed was our recent submission (June 2005) of the Cyphenothrin + Methoprene Squeeze-On for Dogs (2517-ON). Sergeant's explained that this application was submitted as a new end-use product with a 6-month review timeframe; however, the Agency reclassified it to an 18-month review timeframe based on the two pending spot-on applications. We explained that the only new data associated with this submission are product chemistry data and we have cited previously submitted data for the other requirements. We further explained that the previously submitted data was generated on a combination product that contained cyphenonthrin, pyriproxyfen, and methoprene, so that it would support the registration of the various formulations. We then discussed the options we have available. The first option is to withdraw the pending application and resubmit it once the Agency approves the two pending applications. We will then fit into a 6-month review schedule. The second option is to leave the application in EPA with the idea that the Agency will review the product chemistry data in a timely manner and register the product soon after it registers the two pending applications. The Agency

agreed that the second option is probably the better of the two. Ms. Collantes (HED) requested that we send a copy of the product label so that they can include it in the risk assessment they are conducting. It was agreed that a label will be submitted via email and we confirmed that the application rate and uses are identical to what HED is already assessing.

Sergeant's Equine Spot-On (2517-84)

The next product discussed was the recently registered Sergeant's Equine Spot-On (2517-85). Sergeant's thanked EPA for the registration but stated that the product is not marketable with the limited claims the Agency approved. Sergeant's explained that there are not any clear guidance or protocols available to conduct equine efficacy data. They stated that the data submitted to EPA in support of this registration compared their product against an EPA registered positive control. In all cases, Sergeant's products performed equally or better than the EPA registered positive control. Sergeant's further explained that the EPA registered positive control makes claims that Sergeant's had to remove from its label. It was agreed that Sergeant's would submit a written response to EPA explaining the comparison data in more detail and requesting that EPA allow additional label claims comparable to those on the currently registered product. It was also agreed that Sergeant's plans to conduct additional efficacy to expand the label claims. It was agreed that this additional data could be generated within an appropriate timeframe (estimated at 18 months) in order to allow testing during the typical use season. Sergeant's agreed to submit a protocol to EPA for the additional work, so that the Agency can review and comment on it. The Agency agreed to review this information and respond to Sergeant's

Competitive Product

The last topic of discussion related to a competitor of Sergeant's. It has come to Sergeant's attention that a competitor is withdrawing one of its cat spot-on products due to toxicity issues. It is understood that the phase-out on this product is underway. Sergeant's has learned that this competitor may be actively marketing an unregistered replacement pesticide product and that their competitor is announcing to the trade that it has an agreement in place with EPA to review the replacement product in a 45-90 day timeframe. Sergeant's wanted to know if this is true and if there is anything that can be done about the active marketing of an unregistered pesticide product. The Agency stated that they could not discuss the specifics but that there is an agreement with one of Sergeant's competitors. No additional information was discussed.

Sergeant's thanked EPA for taking the time to meet with them and then the meeting was adjourned.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 20, 2005

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP Decision Number: D-345654
EPA File Symbol or Registration Number: 2517-IL
Product Name: SERGEANT'S CYPHENOTHRIN SQUEEZE-ON FOR DOGS
EPA Receipt Date: 29-Jun-2004
EPA Company Number: 2517
Company Name: SERGEANT'S PET CARE PRODUCTS, INC.

STEVEN E. ROGOSHESKE
SERGEANT'S PET CARE PRODUCTS, INC.
D/B/A SERGEANT'S PET PRODUCTS
1479 W POND RD
EAGAN, MN 55122-

SUBJECT: Receipt of Registration Service Fee Voluntary Payment Notice

Dear Registrant:

The Office of Pesticide Programs has received your Notice of Intent to Submit Voluntary Payment for the action described below.

The Action has been re-classified as Action Code: R26.4

NEW USE;NON-FOOD;INDOOR;

Payment in the amount of $4,000 has been received. No additional payment is due for this action.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 305-6249.

Sincerely,

Lois Rossi, Director
Registration Division

Linda Arrington/DC/USEPA/US
05/19/05 04:08 PM

To John Jamula/DC/USEPA/US@EPA
cc George LaRocca/DC/USEPA/US@EPA
bcc
Subject Re: Fw: EPA File Symbol 2517-IU, IN, IL - Change PRIA code

Hi John,

The managers decided that no additional money would be required for these actions. Therefore please reduce the fee to $4000.00 so that the time can start. [redacted]. An new bill can be sent that saying that no additional fee is required.

Thanks

Linda Arrington
Registration Division
703 305 6249
703 305 6920 (fax)
John Jamula/DC/USEPA/US

John Jamula/DC/USEPA/US
05/18/2005 09:01 AM

To Linda Arrington/DC/USEPA/US@EPA
cc
Subject Re: Fw: EPA File Symbol 2517-IU, IN, IL - Change PRIA code

Linda,

2517-IN and 2517-IL have been changed. 2517-IU has not been changed, and is due today.

Revised bills have not been sent..... Let me know when to send them.... Also, for the next several weeks, I will be reviewing contract proposals. During that time, please send revised billing requests to Bob. JJ.
Linda Arrington/DC/USEPA/US

Linda Arrington/DC/USEPA/US
05/18/05 07:36 AM

To John Jamula/DC/USEPA/US@EPA
cc
Subject Fw: EPA File Symbol 2517-IU, IN, IL - Change PRIA code

JJ,

Per George's note, please change 2517-IN and 2715-IL to R26. Please do not send a new bill yet, we need to make the category change today because the action is due today under the wrong code.

Thanks.

Linda Arrington
Registration Division
703 305 6249
703 305 6920 (fax)

----- Forwarded by Linda Arrington/DC/USEPA/US on 05/18/2005 07:28 AM -----

George LaRocca/DC/USEPA/US
05/12/2005 03:35 PM

To Linda Arrington/DC/USEPA/US@EPA
cc
Subject Fw: EPA File Symbol 2517-IU, IN, IL - Change PRIA code

Linda - I spoke with Jim Messina and he has agreed to the change in PRIA code to R-26 for 2517-IN and IL. Keep 2517-IU the same since it is not affected by the residential risk asesment. Thanks.

George LaRocca, PM 13
Insecticides Branch
Registration Division
Office of Pesticides Programs, US EPA
703-305-6100
larocca.george@epa.gov
Visit: http://www.epa.gov/pesticides/

----- Forwarded by George LaRocca/DC/USEPA/US on 05/12/2005 03:28 PM -----

George LaRocca/DC/USEPA/US
05/12/2005 08:21 AM

To Linda Arrington/DC/USEPA/US
cc Marion Johnson/DC/USEPA/US@EPA
Subject EPA File Symbol 2517-IU, IN, IL - Change PRIA code

Hi Linda - I just received confirmation from HED that the subject end use products are considered new uses, non-food indoor actions under R-26 rather than R-31. This is consistent with the action code assigned to the [redacted]. Can you have these codes changed to R-26 and determine if additional monies are needed? I will call Jim Messina if you like. Thanks.

FEE

DATE OUT: 03/FEB/2005

FEE: PRODUCT CHEMISTRY REVIEW OF: Manufacturing-Use [ ] End-Use Product [X]
DP BARCODE:D305951 EPA RECEIVED DATE:27/JUL/2004 F ILE SYMBOL/REG:2517-IL
PRODUCT: Sergeant's Cyphenothrin Squeeze-On For Dogs **MRIDs #463038-01 & -02 ACTION R31**
COMPANY : Sergeant's Pet Care Products, Inc. **NON-FOOD USES [X] DECISION NO.:** 345654
PPC NUMBER OF THE TGAI IN THE PRODUCT: 129013

FROM: Sami Malak, Chemist
Technical Review Branch/RD (7505C)

02-03-05

TO; 13 George LaRocca/Linda DeLuise
Insecticide Branch/RD (7505C)

INTRODUCTION:

In a letter dated 16/JUN/2004, Brazos Associates, Inc. an agent for the applicant requested registration of subject product. In support of this action, the applicant included product chemistry data, a proposed label EPA received on 20/JUN/2004, a proposed basic CSF dated 16/JUN/2004, Formulator's Exemption, Certificate with respect to Citation of Data, and data Matrix..

FINDINGS:

1a. The subject product was produced by a non-integrated formulation system, meaning that the active ingredient in the product is registered. The product contains 40% Cyphenothrin, Reg. No. [redacted].

1b. The subject product, an insecticide, is intended for insect control infesting dogs and puppies older than 12 weeks.

2a. The applicant should be advised to submit product chemistry data requirements pertaining to the storage stability (GRN 830.6317) and corrosion characteristics (GRN 830.6320) identified in this memorandum as data gaps.

2b. Except for the data gaps in Finding 2(a) above, the submitted/referenced product chemistry data is adequate and support registration of subject product.

3. Adequate analytical method is available for enforcement. The method was previously submitted and reviewed in connection with registration of the technical sources, Cyphenothrin, Reg. No. [redacted]

4. The label claim nominal concentrations of 40% Cyphenothrin is consistent with that in the submitted basic CSF dated 16/JUN/2004, both are in compliance with the regulations of PR Notice 91-2. Further, the storage and disposal statement and the physical or chemical hazards statement are in compliance with the regulations of 40CFR§156.78.

5. The proposed basic CSF dated 16/JUN/2004, was filled out correctly in compliance with the regulations of PR Notice 91-2. Further, the upper and lower certified limits are within the standard limits of 40CFR§158.175(b)(2). All ingredients claimed in the CSF are cleared for use in pesticide formulations intended for non-food uses.

CONCLUSIONS: After resolving Findings 2(a) above, the TRB will have no objections for registration of subject product.

REVIEW OF PRODUCT CHEMISTRY DATA:

1. A statement of data confidentiality dated 16/JUN/2004 was included with this submission claiming confidentiality of some of the submitted data on the basis of its falling within the scope of FIFRA§10(d)(1)(A), (B), or (C). Review of CBI data has been removed to Confidential Appendix A.

2. A GLP statement dated 23/JUN/2004 was included with this submission to the effect that some of the submitted studies were conducted in compliance with the GLP requirements of 40CFR§160.

DATA SUBMITTED

Group A, Series 830-Product Identity, Composition, and Analysis (40 CFR 155, 160, 162, 167, 175 & 180)

830-1550 Product Identity and Composition

This product contains one registered technical grade of an active ingredient plus cleared inert ingredients intended for non-food uses (refer to product's basic CSF dated 16/JUN/2004).

830-1600 Description of Materials Used to Produce the Product:
Refer to Confidential appendix A.

830-1650 Description of Formulation Process:
Refer to Confidential appendix A.

830-1670 Discussion of Formation of Impurities:
Refer to Confidential appendix A.

830-1700 Preliminary Analysis:
Refer to Confidential appendix A.

830-1750 Certified Limits:
Refer to Confidential appendix A.

830-1800 Enforcement Analytical Method:

Adequate analytical method is available for enforcement. The method was previously submitted and reviewed in connection with registration of the technical sources, Cyphenothrin, Reg. No. [redacted]

Identity, Composition, Formulation, and Analysis, Subgroup A, Series 830.1550 to 830.1800 (40 CFR 158.155 to 158.180)

Guideline Reference NO.(GRN 830.)/Title	Data Fulfilled	MRID No.
.1550 Product identity and composition	Y	463038-01
.1600 Description of materials used to produce the product	Y	463038-01
.1650 Description of formulation process	Y	463038-01
.1670 Discussion of formation of impurities	Y	463038-01
.1700 Preliminary analysis	Y	463038-01
.1750 Certified limits	Y	463038-01
.1800 Enforcement analytical method	Y	463038-01

Physical and Chemical Properties, Subgroup B, Series 830.6302 to -830.7300 (40 CFR 158.190)

Guideline Reference NO.(GRN 830.)/Title	Data Fulfilled	Value or Qualitative Description	MRID No.
.6302 Color	Y	Clear golden yellow.	463038-02
.6303 Physical state	Y	Liquid.	463038-02
.6304 Odor	Y	Sharp sweet smell, slightly irritating.	463038-02
.6314 Oxidation/seduction: Chemical incompatibility	NA	Does not contain an oxidising or reducing agents.	
.6315 Flammability/flame extension	Y	>200°F.	463038-02
.6316 Explodability	NA	Not considered to be explosive.	
.6317 Storage stability	G		
.6319 Miscibility	Y	Completely miscible in aromatics, petroleum distillates and alcohols. Immiscible in water.	463038-02
.6320 Corrosion characteristics	G		
.6321 Dielectric breakdown voltage	NA	It is not recommended for use around electrical equipment.	
.7000 pH	NA	Insoluble in water.	
.7100 Viscosity	Y	94.5 cps @ 23°C.	463038-02
.7300 Density/relative density/bulk density	Y	1.076 @ 20°C.	463038-02

Explanations: Y =The requirements were fulfilled; N = The requirements not fulfilled; N/A = Not applicable; G = Data gap; U = Requires upgrading; I = Incomplete or in progress; W = Waived.

Confidential Appendix A

830-1600 Description of Materials Used to Produce the Product:

One registered technical grade of an active ingredient plus cleared inert ingredients intended for non-food uses (refer to product's basic CSF dated 12/OCT/2004).

830-1650 Description of Formulation Process:

[redacted]

830-1670 Discussion of Formation of Impurities:

The applicant reported no impurities $\geq$0.1% by weight were known to be formed during formulation and storage of the product. There was no chemical reaction in the process.

830-1700 Preliminary Analysis:

The submitted results of preliminary analysis agree with the label claim nominal concentrations of the active ingredients in the product.

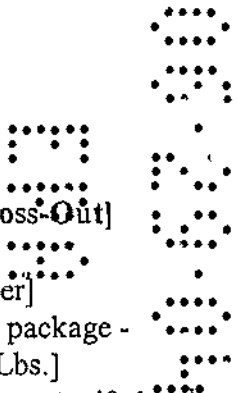
830-1750 Certified Limits:

The applicant reported the same certified limits as those in product's CSF, a basic formulation dated 16/JUN/2004.

cc:S. Malak and Central File (Reg. No. 2517-IL).
7505C:RD:TRB:CM-2:Rm.268:s.m.03/FEB/2005:703-308-9365:<2517-IL>.

[MASTER CARTON/PACK LABEL - FRONT PANEL]

Sergeant's Cyphenothrin Squeeze-On For Dogs



• **DO NOT USE ON CATS [Box/Icon with Cat Image and Cross-Out]**
[• Pleasant Fresh Scent [or][Fragrance]]
[• Flea & Tick Control for Dogs & Puppies 12 weeks old and older]
[• ?? {?? - dependent on applicator size and quantity in market package - "e.g.3, 6 or 12 Months"}Supply][For Dogs Weighing Up To ?? Lbs.]
[• Three Way Protection [Kills fleas, ticks, and mosquitoes]] [for up to 42 days] [per application]
[•Three Way Protection to [Kills fleas, ticks, and mosquitoes]]
[•3 Way Protection! Kills ticks, & mosquitoes]
[• Extended Protection] [[42-Day] [6 Week] [Flea ,Tick & Mosquito Treatment]
[• 42-Day Flea and Tick Control]
[• For Dogs & Puppies (Over 12 Weeks of Age) Less than 15 lbs.]
[• For Dogs & Puppies (Over 12 Weeks of Age) 15 to 33 lbs.]
[• For Dogs & Puppies (Over 12 Weeks of Age) 33 to 66 lbs.]
[• For Dogs & Puppies (Over 12 Weeks of Age) 66 lbs and Over]
[• Three Applications {for cartons with 3 applicators}.] and/or [4-1/2 Month Supply] or [18 Week Supply]
[• For Dogs [less than 15 lbs.] or [15 lbs. to 33 lbs.] or [33 lbs. to 66 lbs.] or [66 lbs. and Over]
[• Best if used year round!]
[• Kills & Repels Fleas Up to [6 weeks], [42 days!]
[• Kills & Repels New Fleas in less than 1 hour!]
[• Kills & Repels New Ticks in less than 3 hours!]
[• Kills & Repels 95% of Fleas and Ticks [and continues to work for up to six weeks]
[• Kills 99% of Fleas one day after application]
[• Prevents ticks from attaching and feeding within 3 hours after application]
[• 95% efficacy against ticks for up to[6 weeks] [42 days]
[• Kills and Detaches Ticks]
[• Kills over 95% of Ticks]
[• Easy to Use Application]
[• Specially Formulated for Dogs and Puppies]
[• Patented Technology [combines effectiveness with gentleness!]]
[• 42 Day Protection!]
[• Monthly Calendar Stickers Inside!]
[• Kills Mosquitoes for up to [30 days!] [42 days!]
[• Kills Mosquitoes (vector of West Nile Virus) for up to [30 days] [42 days!]

[• Protects Against Blood Feeding by Mosquitoes (vector of Heartworm) For up to [30 days!] [42 days!]
[• Kills & Repels Ticks for Up to [42 days],[6 weeks]!]
[• Kills & Repels Deer Ticks (vector of Lyme Disease) for up to [35 days!] [42 days!]
[• Kills & Repels Ticks (Including Deer Ticks) for up to [35 days!] [42 days!]
[• Kills & Repels Brown Dog Ticks [(*Rhipicephalus sanguineus*)] for up to 42 days!]
[• Kills & Repels American Dog Ticks [(*Dermacentor variabilis*)] for up to 42 days!]
[• Apply every [42 days], [6 weeks]!]
[• 42 Days Flea and Tick Treatment!]
[• Kills & Repels Fleas and Ticks for up to 42 days!]
[• Kills & Repels Mosquitoes that are vectors of West Nile Virus.]
[• Waterproof formula.]
[• Dogs can be bathed 24 hours after squeeze-on is applied]
[• Continues to work 50% longer than other leading brands]
[• Longest lasting, quick acting]

[• May contain graphics illustrating product use, e.g., dog with a drop falling onto its neck from a vial on front, side, or back carton label and/or applicator labeling.]

[ ] - Denotes Optional Statements and/or Images that May be Used on Front, Back or Side Label Panels.

ACTIVE INGREDIENTS:	
Cyphenothrin (CAS# 39515-40-7)	40.0%
OTHER INGREDIENTS:	60.0%
TOTAL:	100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See [Back][or][Side] Label Panel[s] for Additional Precautionary Statements

NET CONTENTS: **[THREE][SIX][TWELVE] 1.0 ml Tubes**
[THREE][SIX][TWELVE] 1.5 ml Tubes
[THREE][SIX][TWELVE] 3.0 ml Tubes
[THREE][SIX][TWELVE] 4.5 ml Tubes

[MASTER CARTON/PACK LABEL - BACK/SIDE PANELS]

Sergeant's Cyphenothrin Squeeze-On For Dogs

[DO NOT USE ON CATS] [Box/Icon with Cat Image and Cross-Out]

READ ENTIRE LABEL BEFORE EACH USE.
USE ONLY ON DOGS AND PUPPIES OVER 12 WEEKS OF AGE.
DO NOT USE ON CATS

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS AND DOMESTIC ANIMALS

CAUTION: Harmful if swallowed or absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling. FOR EXTERNAL USE ON DOGS ONLY. Do not use on puppies under 12 weeks of age. Consult a veterinarian before using this product on debilitated, aged, medicated, pregnant, or nursing dogs. Consult a veterinarian before using on dogs with known organ dysfunction. DO NOT USE ON CATS or animals other than dogs. Cats that actively groom or engage in close physical contact with treated dogs may be at risk of serious harmful effects. Sensitivities may occur after using ANY pesticide product on pets. If signs of sensitivity occur bathe your dog with a mild soap and rinse with large amounts of water. If signs continue, consult a veterinarian immediately.

FIRST AID	
If in eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If swallowed	• Immediately call a poison control center or doctor. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give **any** liquid to the person. • Do not give anything by mouth to an unconscious person.
If on skin or clothing	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice.

HOTLINE NUMBER

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-224-PETS [or][x-xxx-xxx-xxxx] for emergency medical treatment information.

NOTE TO PHYSICIAN OR VETERINARIAN

Treat patient symptomatically

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
DO NOT USE ON CATS. May be toxic and potentially fatal if applied to or ingested by cats.

How to apply: Remove product tube from package. Holding tube with top end pointing up and away from face and body, snap or cut off top end. Invert tube over dog and use open end to part dog's hair. Squeeze tube firmly to apply all of the solution to the dog's skin, as directed below. Repeat application may be made if necessary, but do not apply more often than once every 4 weeks.

For Dogs Weighing 15 lbs. and Under: {For cartons containing 1.0 ml applicator tubes}
Apply one tube (1.0 ml) as a spot or stripe to the dog's back between the shoulder blades.

For Dogs Weighing Between 15 and 33 lbs. {For cartons containing 1.5 ml applicator tubes}
Apply one tube (1.5 ml) as a spot or stripe to the dog's back between the shoulder blades.

For Dogs Weighing Between 33 and 66 lbs. {For cartons containing at least two 1.5 ml applicator tubes, or at least one 3.0 ml applicator tube}
[Apply two tubes (1.5 ml) as a spot or stripe to the dog's back between the shoulder blades and apply the second tube as a spot or stripe to the dog's back directly in front of the base of the tail.} - or - [Apply one tube (3.0 ml) as a continuous stripe on the dog's back starting between the shoulder blades and ending directly in front of the base of the dog's tail.]

For Dogs Weighing 66 lbs. and Over: {For cartons containing at least three 1.5 ml applicator tubes, or at least one 4.5 ml applicator tube}
[Apply the first tube (1.5 ml) as a spot or stripe to the dog's back between the shoulder blades and apply the contents of the other two tubes (1.5 ml each) along the dog's back extending to directly in front of the base of the tail.] - or - [Apply one tube (4.5 ml) as a continuous stripe on the dog's back starting between the shoulder blades and ending directly in from of the base of the dog's tail.]

[MASTER CARTON/PACK LABEL - BACK/SIDE PANELS]

STORAGE AND DISPOSAL

STORAGE: Do not remove tube from the pack until ready to use. Store in a cool (below 25°C) dry place inaccessible to children and pets. Do not refrigerate. Protect from direct sunlight.

DISPOSAL: If empty: Do not reuse this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-CLEANUP for disposal instructions. Never place unused product down any indoor or outdoor drain.

[Sergeant's Cyphenothrin Squeeze-On For Dogs is an effective and easy to use product.] [Sergeant's Cyphenothrin Squeeze-On For Dogs has demonstrated that greater than 95% control of fleas and ticks are killed within one day of application.] [As with all flea and tick control products, Sergeant's Cyphenothrin Squeeze-On For Dogs should be used as part of a program aimed at reducing flea populations in the dog's environment (bedding, carpets, kennel, yard).] [Consult your retailer for program recommendations.]

[www.sergeants.com]

MADE IN
USA

[Sergeant's is committed to providing high quality products. If you have questions or comments about this product, please write: Sergeant's Consumer Response; P.O. Box 540399; Omaha, NE 68154-0399.]

[Satisfaction Guaranteed!] [Please return for a refund if not completely satisfied!]

[In Case of Emergency, call 1-800-224-PETS.]

[WARRANTY: SERGEANT'S PET CARE PRODUCTS, INC. MAKES NO WARRANTY OF MERCHANTABILITY, FITNESS FOR ANY PARTICULAR PURPOSE, OR OTHERWISE, EXPRESSED OR IMPLIED, CONCERNING THIS PRODUCT OR ITS USES WHICH EXTEND BEYOND THE USE OF THE PRODUCT UNDER NORMAL CONDITIONS IN ACCORDANCE WITH THE STATEMENTS MADE ON THIS LABEL.]

Made in the USA For:
Sergeant's Pet Care Products, Inc.
Omaha, NE 68130
EPA Reg. No. 2517 -XX
EPA Est. No. XXXXX -XX -XXX

[BAR CODE AREA]

[TUBE/APPLICATOR LABEL]

FRONT PANEL -

Sergeant's Cyphenothrin Squeeze-On For Dogs, [Box/Icon with Cat Image and Cross-Out], [1.0 ml] or [1.5 ml] or [3.0 ml] or [4.5 ml], Active Ingredients: Cyphenothrin 40.0%; Other Ingredients: 60.0%

BACK PANEL -

READ DIRECTIONS/PRECAUTIONS BEFORE USING.
CAUTION: KEEP OUT OF REACH OF CHILDREN
EPA REG. NO. 2517-XX

Revised 06/16/2004:
S:\Main\Sergeant's Pet Products\Labels\Sergeant's Cyphenothrin Squeeze-On For Dogs.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

June 30, 2004

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PLEASE RETURN A COPY OF THIS LETTER WITH PAYMENT

OPP Decision Number: D-345654
EPA File Symbol or Registration Number: 2517-IL
Product Name: SERGEANT'S CYPHENOTHRIN SQUEEZE-ON FOR DOGS
EPA Receipt Date: 29-Jun-2004
EPA Company Number: 2517
Company Name: SERGEANT'S PET CARE PRODUCTS, INC.

MARLA K. JACKSON
BRAZOS ASSOCIATES, INC
SERGEANT'S PET CARE PRODUCTS, INC.
1806 AUBURN DRIVE
CARROLLTON, TX 75007-1451

SUBJECT: Receipt of Registration Application Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your application for registration. If you submitted data with this application, the results of the PRN-86-5 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R31

NEW PRODUCT;NON-FAST TRACK (INCLUDES REVIEWS OF PRODUCT CHEMISTRY;ACUTE TOXICITY;PUBLIC HEALTH PEST EFFICACY);

Please remit payment in the amount of: $ 4,000 to:

By USPS:
USEPA Washington Finance Center
Pesticide Registration Service Fee
PO Box 360277
Pittsburgh, PA 15251

By Courier:
U.S. EPA Washington Finance Center
Pesticide Registration Service Fee
C/O Mellon Client Service Center
500 Ross Street, Room 670
Box 360277
Pittsburgh, PA 15251-6277
Attn: EPA Module Supervisor
Telephone: (412) 236-2294

All payments must be in United States currency by check, bank draft, or money order drawn to the order of the Environmental Protection Agency. To ensure proper credit, please write the OPP DECISION NUMBER on your check, and enclose a copy of this letter with your payment.

You may be eligible for a full or partial waiver of the registration service fee if, for example, you qualify as a small business or are applying for a minor use, or if your application is solely associated with an IR-4 tolerance petition. Please be advised that if you intend to request a waiver, you must do so in writing within 15 days of receipt of this invoice instead of remitting the amount indicated above. OPP will not consider waiver requests after the registration service fee has been paid. Information regarding eligibility and how th request and document a fee waiver is available on the OPP Fee for Service web site at www.epa.gov/pesticides/fees.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 305-6249.

Sincerely,

James A. Hollins

Front End Processing Staff
Information Resources and Services Division

Fee for Service

This package includes the following

- [X] New FFS Action
- [ ] Amendment
- [ ] Waiver Request
- [ ] Voluntary Payment Request

for Division

- [X] RD
- [ ] AD
- [ ] BPPD

Receipt Nos. S- 762874

Product/Risk Manager: 13

EPA File Symbol/Reg. No. 2517-IL

Pin-Punch Date: 6/29/04

☐ This item is NOT subject to FFS action.

Action Code: ~~R352~~ R-31

Amount Due: $ ~~[illegible]~~ 4,000

Voluntary Payment Reduction Amount:

☐ 0%	☐ 40%	☐ 80%	Original Decision #:
☐ 10%	☐ 50%	☐ 90%	
☐ 20%	☐ 60%	☐ 100%	
☐ 25%	☐ 70%	☐ Other	D- _____
☐ 30%	☐ 75%	____%	

Reviewer: J. Miller Date: 6/30/04

Remarks: Appears to be a New formulation and a ~~a~~ use pattern not previously approved ~~for~~ this AI.

Brazos Associates, Inc.®

1806 Auburn Drive • Carrollton, Texas 75007-1451
Phone: 972-939-8390 • Facsimile: 972-939-8370
E-mail: marla@brazosassociates.com

June 16, 2004

Document Processing Desk (REGFEE)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Room 266A, Crystal Mall #2
1801 South Bell Street
Arlington, VA 22202

Attn: Mr. George T. LaRocca
Product Manager Team 13

Dear Mr. LaRocca:

RE: Sergeant's Cyphenothrin Squeeze-On For Dogs
EPA Company Number: 2517

This submission for a new registration is being made on behalf of our client, Sergeant's Pet Care Products, Inc. ("Sergeant's"). With this submission, we are utilizing the "Selective Method" of data support and are relying on data developed by Sergeant's as well as data from the McLaughlin Gormley King Company ("MGK Company").

The above referenced proposed product registration contains the active ingredient, Cyphenothrin at 40% a.i. Cyphenothrin is not currently registered for direct application to dogs. However, Cyphenothrin is approved under the General Use-Patterns, "Indoors - Pets", as a fogger, and spray for treatment of pet bedding, pet sleeping quarters, and pet living quarters for control of fleas, ticks, flies and mosquitoes. Such pet treatment uses can be found on approved labeling for the following registrations: EPA Reg. No's 1021-1681, 1021-1684, 1021-1685, 1021-1686, 1021-1765 and 4822-393.

As Cyphenothrin is currently approved under the General Use Pattern of "Indoors - Pets" for treatments made via foggers or spray, we do not believe the use of Cyphenothrin directly on pets ("dogs") would not be meet the definition of a new use as defined in 40 CFR Part 152.3. For this reason we believe the appropriate Fee Category is R31 for the Fee Amount of $4,000.

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060. Approval expires 2-28-95

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☑ Registration
☐ Amendment
☐ Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
2517-IL	George T. LaRocca	☑ None ☐ Restricted
4. Company/Product (Name)	**PM#**	
Sergeant's Cyphenothrin Squeeze-On for Dogs	13	

5. Name and Address of Applicant *(Include ZIP Code)*

Sergeant's Pet Care Products, Inc.
2637 South 158 Plaza, Suite 100
Omaha, NE 68130-1703

☐ *Check if this is a new address*

6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(ii, my product is similar or identical in composition and labeling to:
EPA Reg. No. _____
Product Name _____

Section - II

☐ Amendment - Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application.
☑ Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Application for Registration of a New End-Use Pesticide Product Registration Containing a Registered Active Ingredient.

REGISTRATION FEE: We believe the correct Registration Fee Code for the registration action is "R31", and the correct Registration Fee Amount is $4,000. Please notify us with regards to confirmation of fee amount by e-mail to: michael@brazosassociates.com, or by fax at 972-939-8370.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes ☑ No	☑ Yes ☐ No	☐ Yes ☑ No	☐ Metal ☑ Plastic ☐ Glass ☑ Paper ☐ Other (Specify) _____
** Certification must be submitted*	If "Yes" Unit Packaging wgt.: f.0 to 4.5 ml; No. per container: t to 3	If "Yes" Package wgt: ; No. per container:	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☑ Label ☐ Container	1.0, 1.5, 3.0 and 4.5 ml	☐ Outer Carton

6. Manner in Which Label Is Affixed to Product ☑ Lithograph ☐ Paper glued ☐ Stenciled ☑ Other Printed - Outer Carton

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
Marla K. Jackson	Agent for Sergeant's Pet Care Products, Inc.	972-939-8390

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

2. Signature	3. Title	6. Date Application Received
Marla K. Jackson	Agent for Sergeant's Pet Care Products, Inc.	(Stamped)
4. Typed Name	**5. Date**	
Marla K. Jackson	06/16/2004	

EPA Form 8570-1 (Rev. 3-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

Included with this request for a new end-use pesticide registration please find the following:

1. EPA Application for Pesticide Registration (EPA Form 8570-1)
2. Transmittal Document/Bibliography of Submitted Data
3. Letter of Consultant Authorization from Sergeant's Pet Care Products, Inc.
4. Letter of Data Support from MGK Company
5. EPA Formulator's Exemption Statement (EPA Form 8570-27)
6. EPA Confidential Statement of Formula (EPA Form 8570-4)
7. Certification of Certified Limits of Ingredients
8. EPA Certification with Respect to Citation of Data (EPA Form 8570-34)
9. EPA Data Matrix (Agency & Public File Copies)(EPA Form 8570-35)
10. Five (5) Copies of Proposed Product Labeling

Three (3) Copies each of the following Data/Studies:

11. Product Properties Data Entitled: *"Product Properties Data (Groups "A") on Sergeant's Cypenothrin Squeeze-On for Dogs"*. OPPTS Test Guidelines: 830.1550, 830.1600, 830.1620, 830.1650, 830.1670, 830.1750 and 830.1800.
12. Product Properties Data Entitled: *"Product Chemistry of Gokilaht Spot-On F-2829"*. OPPTS Test Guidelines: 61-1 to 61-3, 62-1 to 62-3 and 63-2 to 63-21.
13. Acute Inhalation Study Data Waiver Request Entitled: *"Sergeant's Cyphenothrin Squeeze-On for Dogs Waiver Request from the Requirement to Conduct Acute Inhalation Data - 870.1300"*. OPPTS Test Guideline: 870.1300.

We trust you will find everything in order with this submission. Should you have any questions or need additional information please do not hesitate to contact us.

Sincerely,

Marla K. Jackson
Agent for Sergeant's Pet Care Products, Inc.

cc: Mr. Larry Nouvel - Nouvel & Associates, Inc.
Ms. Caryn Stichler - Sergeant's Pet Care Products, Inc.

TRANSMITTAL DOCUMENT
BIBLIOGRAPHY OF SUBMITTED DATA

Submitter: Sergeant's Pet Care Products, Inc.
2637 South 158th Plaza, Ste. 100
Omaha, NE 68130-1703

Product Name: Sergeant's Cypenothrin Squeeze-On for Dogs
"Application for New Product Registration"

EPA Company Number: 2517

Transmittal Date: June 16, 2004

Volume	Data Description	MRID Number
1 of 3	Jackson, M. K. (2004). *"Product Properties Data (Group "A") on Sergeant's Cyphenothrin Squeeze-On for Dogs"*. OPPTS Test Guidelines 830.1550, 830.1600, 830.1620, 830.1650, 830.1670, 830.1750 & 830.1800. Unpublished Study by Brazos Associates, Inc.; 1806 Auburn Drive; Carrollton, TX 75007-1451. 6 pages and 6 pages.	_____
2 of 3	Besser, B. D. (2003). *"Product Chemistry of Gokilaht Spot-On F-2829"*. Guideline Numbers 61-1 to 61-3, 62-1 to 62-3, 63-2 to 63-21. Unpublished Study by McLaughlin Gormley King Company; 8810 Tenth Avenue North; Minneapolis, MN 55427. 8 pages.	_____
3 of 3	Jackson, M. A. (2004). *"Sergeant's Cyphenothrin Squeeze-On For Dogs Waiver Request from the Requirement to Conduct an Acute Inhalation Study-870.1300"*. Unpublished Study (Request) by Brazos Associates, Inc.; 1806 Auburn Drive; Carrollton, TX 75007-1451. 6 pages.	_____

Sergeant's
Pet Care Products, Inc.

March 11, 2004

Document Processing Desk (COADR)
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202-4501

Attn: Ms. Lois Rossi, Director
Office of Pesticide Programs – Registration Division

Dear Ms. Rossi:

Subject: Authorized Agents

Sergeant's Pet Care Products, Inc. (EPA Company Number: 2517) hereby appoints the following party as its primary agent of record to handle all registration matters on our behalf before the U.S. Environmental Protection Agency:

Mr. Steven E. Rogosheske
Rogosheske Consulting
1479 West Pond Road
Eagan, MN 55122

Phone: 651-330-1217
Fax: 651-330-1217
E-mail: srogo@comcast.net

In addition, representatives for the company named below are authorized to handle registration matters on behalf of Sergeant's Pet Care Products, Inc. including, but not limited to, filing of submissions, direct correspondence with Agency Officials via phone, fax, e-mail, etc., responding to or addressing other FIFRA related regulatory issues:

Brazos Associates, Inc.
1806 Auburn Drive
Carrollton, TX 75007-1451

Phone: 972-939-8390
Fax: 972-939-8370
E-mail: michael@brazosassociates.com

These appointments and authorization for Agent's supersedes all others as previously provided by Sergeant's Pet Care Products, Inc. (D.B.A. "Sergeant's Pet Products") and will remain in effect until revoked in writing by our firm. Should you have any questions, please do not hesitate to contact me.

Sincerely,

Joel Adamson
Senior Vice President Marketing

Notary Public

JO ANN KRENISKY
GENERAL NOTARIAL
SEAL
STATE OF NEBRASKA
Commission Expires
Sept. 28, 2006

MGK®
McLAUGHLIN GORMLEY KING COMPANY
8810 Tenth Avenue North • Minneapolis, MN 55427-4319 U.S.A.
763-544-0341 • 800-645-6466 • Fax 763-544-6437 • www.mgk.com

April 5, 2004

Mr. George LaRocca, PM13
Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue N.W.
Washington DC 20460-0001

Subject: Letter of Authorization

Dear Mr. LaRocca:

This letter serves as authorization, in accordance with our agreement with the registrant, to refer to the following data submitted to EPA for the subject company's registration.

Product Name: "Sergeant's Cyphenothrin Squeeze-On For Dogs"
Registrant Name & Address: Sergeants Pet Care Products, Inc.
2637 South 158th Plaza, Ste. 100
Omaha, NE 68130-1703

EPA Company Number: 2517

Product Properties Data: Study Titles/Information -

1 Study Title/Information - Study Title: Product Chemistry of Gokilaht Spot-On (F-2829); Test Guidelines: 61-1 through 63-21; Performing Laboratory: McLaughlin Gormley King Company; Author: Brice Besser; Study No.: GLP-1709. (June 23, 2003)

Acute Toxicology Data: Study Titles/Information -

1. Acute Oral Toxicity Up and Down Procedure In Rats; MRID No. 46166103
2. Acute Dermal Toxicity Study in Rats, Limit Test; MRID No. 46166104
3. Primary Eye Irritation Study in Rabbits: MRID No. 46166105
4. Primary Skin Irritation Study in Rabbits: MRID No. 46166106
5. Dermal Sensitization Study in Guinea Pigs (Buehler Method): MRID No. 46166107

Although this is authorization to rely on MGK data for the subject company's subject registration, absolutely no data of a confidential nature is to be disclosed to them.

Sincerely,

Julie B Schlekau

Julie B. Schlekau
Registration Specialist

Product ingredient source information may be entitled to confidential treatment

Form Approved. OMB No. 2070-0060. Approval Expires 5-31-98.

United States
Environmental Protection Agency
Washington, DC 20460

Formulator's Exemption Statement

(40 CFR 152.85)

Applicant's Name and Address	EPA File Symbol/Registration Number
Sergeant's Pet Care Products, Inc. 2637 South 158 Ptaza, Suite 100 Omaha, NE 68130-1703	2517-
	Product Name Sergeant's Cyphenothrin Squeeze-On For Dogs
	Date of Confidential Statement of Formula *(EPA Form 8570-4)* 6/16/2004

As an authorized representative of the applicant for registration of the product identified above, I certify that:

(1) This product contains the following active ingredient(s):

Cyphenothrin

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the use of that active ingredient in the manufacturing, formulation or repackaging another product which contains that active ingredient which is registered under FIFRA Section 3, is purchased by us from another producer, and is labeled for at least each use for which my product is proposed to be labeled.

(3) Indicate by checking (A) or (B) below which paragraph applies:

☒ (A) An accurate Confidential Statement of Formula *(EPA FORM 8570-4)* for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1).

OR

☐ (B) The Confidential Statement of Formula (CSF) (EPA Form 8570-4) referenced above and on file with the EPA is complete, current, and accurate and contains the information required on the current CSF.

(4) The following active ingredients in this product qualify for the formulator's exemption.

Source

Active Ingredient	Product Name	Registration Number
Cyphenothrin	[redacted]	[redacted]

Signature	Name and Title	Date
Marla K. Jackson	Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc.	6/16/2004

EPA Form 8570-27 (Rev. 8-95)

White - EPA copy
Yellow - Applicant copy

* U.S. GPO: 1996-388-620/20413

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number Sergeant's Pet Care Products, Inc.; 2637 S. 158 Plaza, #100; Omaha, NE 68130; 402-938-7000	EPA Registration Number/File Symbol 2517-
Active Ingredient(s) and/or representative test compound(s) Cyphenothrin	Date 6/16/04
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) Indoor	Product Name Sergeant's Cyphenothrin Squeeze-On for Dogs

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).	☑ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

[Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements]

☐ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses.

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature	Date	Typed or Printed Name and Title
Marla K. Jackson	6/15/04	Marla K. Jackson - Agent for Sergeant's Pet Care Products, Inc.

EPA Form 8570-34 (9-97) Electronic and Paper versions available. Submit only Paper version.

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DATA MATRIX

Date: 6/16/2004	EPA Reg. No./File Symbol: 2517-	Page 1 of 5
Applicant's/Registrant's Name & Address: Sergeant's Pet Care Products, Inc. 2637 South 158th Plaza, Ste. 100 Omaha, NE 68130-1703	Product: Sergeant's Cyphenothrin Squeeze-On for Dogs	

Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guidelines, Group A - Product Identity, Composition, and Analysis of Test Guidelines:					
830.1550	Product Identity and Composition	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1600	Description of Materials Used to Produce the Product	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1620	Description of Production Process	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1650	Description of Formulation Process	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1670	Discussion of Formation of Impurities	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1700	Preliminary Analysis		Not Applicable. Product is not a technical grade material and product is not produced by an integrated formulation system.		
830.1750	Certified Limits	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1800	Enforcement Analytical Method	New Submission	McLaughlin Gormley King Company	PER	
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines:					
830.6302	Color	New Submission	McLaughlin Gormley King Company	PER	
830.6303	Physical State	New Submission	McLaughlin Gormley King Company	PER	
830.6304	Odor	New Submission	McLaughlin Gormley King Company	PER	

Signature: Marla K Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Applicant's/Registrant's Name & Address: Sergeant's Pet Care Products, Inc. 2637 South 158th Plaza, Ste. 100 Omaha, NE 68130-1703	Product: Sergeant's Cyphenothrin Squeeze-On for Dogs	

Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guidelines, Group A - Product Identity, Composition, and Analysis of Test Guidelines:					
[redacted]			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Not Applicable. Product is not a technical grade material and product is not produced by an integrated formulation system.		
			Sergeant's Pet Care Products, Inc.	OWN	
			McLaughlin Gormley King Company	PER	
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines:					
[redacted]			McLaughlin Gormley King Company	PER	
			McLaughlin Gormley King Company	PER	
			McLaughlin Gormley King Company	PER	

Signature: Marla K. Jackson

Name & Title: Marla K. Jackson
Agent for Sergeant's Pet Care Products, Inc

Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guidelines, Group A - Product Identity, Composition, and Analysis of Test Guidelines:					
[redacted]			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Sergeant's Pet Care Products, Inc.	OWN	
			Not Applicable. Product is not a technical grade material and product is not produced by an integrated formulation system.		
			Sergeant's Pet Care Products, Inc.	OWN	
			McLaughlin Gormley King Company	PER	
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines:					
[redacted]			McLaughlin Gormley King Company	PER	
			McLaughlin Gormley King Company	PER	
			McLaughlin Gormley King Company	PER	

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guidelines, Group A - Product Identity, Composition, and Analysis of Test Guidelines:					
830.1550	Product Identity and Composition	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1600	Description of Materials Used to Produce the Product	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1620	Description of Production Process	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1650	Description of Formulation Process	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1670	Discussion of Formation of Impurities	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1700	Preliminary Analysis		Not Applicable. Product is not a technical grade material and product is not produced by an integrated formulation system.		
830.1750	Certified Limits	New Submission	Sergeant's Pet Care Products, Inc.	OWN	
830.1800	Enforcement Analytical Method	New Submission	McLaughlin Gormley King Company	PER	
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines:					
830.6302	Color	New Submission	McLaughlin Gormley King Company	PER	
830.6303	Physical State	New Submission	McLaughlin Gormley King Company	PER	
830.6304	Odor	New Submission	McLaughlin Gormley King Company	PER	

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
830.6313	Stability to Normal and Elevated Temperatures Metals, and Metal Ions		Not Applicable. Not a technical grade product.		
830.6314	Oxidation/Reduction: Chemical Incompatibility		Waiver Requested: Product contains no oxidizing/reduction agents. Further, product is packaged in small (1 to 4.5 ml) containers for single/one time application both of which minimize the potential for contact with other products or materials.		
830.6315	Flammability	New Submission	McLaughlin Gormley King Company	PER	
830.6316	Explodability		Waiver Requested: Based on flash point of >201°F, lack of potentially explosive formulation components, and limited package quantity (1 to 4.5 ml) there is no explosive potential.		
830.6317	Storage Stability		A 1-year Storage Stability Study with 0, 3, 6, 9 and 12 month analysis intervals is currently being conducted on behalf of Sergeant's Pet Care Products, Inc. by McLaughlin Gormley King Company and will be submitted to the Agency on completion.		
830.6319	Miscibility		Not Applicable. Product is not labeled for nor intended to be mixed with petroleum solvents.		
830.6320	Corrosion Characteristics		Test is running in conjunction with Storage Stability Study.		

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
[redacted]			Not Applicable. Not a technical grade product.		
			Waiver Requested: Product contains no oxidizing/reduction agents. Further, product is packaged in small (1 to 4.5 ml) containers for single/one time application both of which minimize the potential for contact with other products or materials.		
			McLaughlin Gormley King Company	PER	
			Waiver Requested: Based on flash point of >201°F, lack of potentially explosive formulation components, and limited package quantity (1 to 4.5 ml) there is no explosive potential.		
			A 1-year Storage Stability Study with 0, 3, 6, 9 and 12 month analysis intervals is currently being conducted on behalf of Sergeant's Pet Care Products, Inc. by McLaughlin Gormley King Company and will be submitted to the Agency on completion.		
			Not Applicable. Product is not labeled for nor intended to be mixed with petroleum solvents.		
			Test is running in conjunction with Storage Stability Study.		

Signature:	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
[redacted]			Not Applicable. Not a technical grade product.		
			Waiver Requested: Product contains no oxidizing/reduction agents. Further, product is packaged in small (1 to 4.5 ml) containers for single/one time application both of which minimize the potential for contact with other products or materials.		
			McLaughlin Gormley King Company	PER	
			Waiver Requested: Based on flash point of >201°F, lack of potentially explosive formulation components, and limited package quantity (1 to 4.5 ml) there is no explosive potential.		
			A 1-year Storage Stability Study with 0, 3, 6, 9 and 12 month analysis intervals is currently being conducted on behalf of Sergeant's Pet Care Products, Inc. by McLaughlin Gormley King Company and will be submitted to the Agency on completion.		
			Not Applicable. Product is not labeled for nor intended to be mixed with petroleum solvents.		
			Test is running in conjunction with Storage Stability Study.		

Signature: Marla K. Jackson

Name & Title: Marla K. Jackson
Agent for Sergeant's Pet Care Products, Inc

Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
830.6313	Stability to Normal and Elevated Temperatures Metals, and Metal Ions		Not Applicable. Not a technical grade product.		
830.6314	Oxidation/Reduction: Chemical Incompatibility		Waiver Requested: Product contains no oxidizing/reduction agents. Further, product is packaged in small (1 to 4.5 ml) containers for single/one time application both of which minimize the potential for contact with other products or materials.		
830.6315	Flammability	New Submission	McLaughlin Gormley King Company	PER	
830.6316	Explodability		Waiver Requested: Based on flash point of >201°F, lack of potentially explosive formulation components, and limited package quantity (1 to 4.5 ml) there is no explosive potential.		
830.6317	Storage Stability		A 1-year Storage Stability Study with 0, 3, 6, 9 and 12 month analysis intervals is currently being conducted on behalf of Sergeant's Pet Care Products, Inc. by McLaughlin Gormley King Company and will be submitted to the Agency on completion.		
830.6319	Miscibility		Not Applicable. Product is not labeled for nor intended to be mixed with petroleum solvents.		
830.6320	Corrosion Characteristics		Test is running in conjunction with Storage Stability Study.		

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
830.6321	Dielectric Breakdown Voltage		Not Applicable. Product is not labeled for use or intended for use around electrical equipment.		
830.7000	pH		Not Applicable. Product is insoluble in water; thus, not dispersible with water.		
830.7050	UV/Visible Absorption		Not Applicable. Product is not a pure active ingredient.		
830.7200	Melting Point/Melting Range		Not Applicable. Product is not a pure or technical grade material.		
830.7220	Boiling Point/Boiling Range		Not Applicable. Product is not a pure or technical grade material.		
830.7300	Density/Relative Density/Bulk Density	New Submission	McLaughlin Gormley King Company	PER	
830.7370	Dissociation Constants in Water		Not Applicable. Product is not a pure active ingredient.		
830.7520	Particle Size, Fiber Length, and Diameter Distribution		Not Applicable. Product physical state is a liquid.		
830.7550	Partition Coefficient (*n*-octanol/water), Shake Flask Method		Not Applicable. Product is not a non-polar organic pure active ingredient.		
830.7560	Partition Coefficient (*n*-octanol/water), Generator Column Method		Not Applicable. Product is not a non-polar organic pure active ingredient.		
830.7570	Partition Coefficient (*n*-octanol/water), Estimation by Liquid Chromatography		Not Applicable. Product is not a non-polar organic pure active ingredient.		

Signature: Marla K Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
[redacted]			Not Applicable. Product is not labeled for use or intended for use around electrical equipment.		
			Not Applicable. Product is insoluble in water; thus, not dispersible with water.		
			Not Applicable. Product is not a pure active ingredient.		
			Not Applicable. Product is not a pure or technical grade material.		
			Not Applicable. Product is not a pure or technical grade material.		
			McLaughlin Gormley King Company	PER	
			Not Applicable. Product is not a pure active ingredient.		
			Not Applicable. Product physical state is a liquid.		
			Not Applicable. Product is not a non-polar organic pure active ingredient.		
			Not Applicable. Product is not a non-polar organic pure active ingredient.		
			Not Applicable. Product is not a non-polar organic pure active ingredient.		

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
[redacted]			Not Applicable. Product is not labeled for use or intended for use around electrical equipment.		
			Not Applicable. Product is insoluble in water; thus, not dispersible with water.		
			Not Applicable. Product is not a pure active ingredient.		
			Not Applicable. Product is not a pure or technical grade material.		
			Not Applicable. Product is not a pure or technical grade material.		
			McLaughlin Gormley King Company	PER	
			Not Applicable. Product is not a pure active ingredient.		
			Not Applicable. Product physical state is a liquid.		
			Not Applicable. Product is not a non-polar organic pure active ingredient.		
			Not Applicable. Product is not a non-polar organic pure active ingredient.		
			Not Applicable. Product is not a non-polar organic pure active ingredient.		

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
Washington, D.C. 20460

DATA MATRIX

Date: 6/16/2004	EPA Reg. No./File Symbol: 2517-	Page 3 of 5
Applicant's/Registrant's Name & Address: Sergeant's Pet Care Products, Inc. 2637 South 158th Plaza, Ste. 100 Omaha, NE 68130-1703	Product: Sergeant's Cypenothrin Squeeze-On for Dogs	

Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
830.6321	Dielectric Breakdown Voltage		Not Applicable. Product is not labeled for use or intended for use around electrical equipment.		
830.7000	pH		Not Applicable. Product is insoluble in water; thus, not dispersible with water.		
830.7050	UV/Visible Absorption		Not Applicable. Product is not a pure active ingredient.		
830.7200	Melting Point/Melting Range		Not Applicable. Product is not a pure or technical grade material.		
830.7220	Boiling Point/Boiling Range		Not Applicable. Product is not a pure or technical grade material.		
830.7300	Density/Relative Density/Bulk Density	New Submission	McLaughlin Gormley King Company	PER	
830.7370	Dissociation Constants in Water		Not Applicable. Product is not a pure active ingredient.		
830.7520	Particle Size, Fiber Length, and Diameter Distribution		Not Applicable. Product physical state is a liquid.		
830.7550	Partition Coefficient (*n*-octanol/water), Shake Flask Method		Not Applicable. Product is not a non-polar organic pure active ingredient.		
830.7560	Partition Coefficient (n-octanol/water), Generator Column Method		Not Applicable. Product is not a non-polar organic pure active ingredient.		
830.7570	Partition Coefficient (*n*-octanol/water), Estimation by Liquid Chromatography		Not Applicable. Product is not a non-polar organic pure active ingredient.		

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Applicant's/Registrant's Name & Address: Sergeant's Pet Care Products, Inc. 2637 South 158th Plaza, Ste. 100 Omaha, NE 68130-1703	Product: Sergeant's Cypenothrin Squeeze-On for Dogs	

Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
830.7840	Water Solubility, Column Elution Method; Shake Flask Method		Not Applicable. Product is not a pure active ingredient.		
830.7860	Water Solubility, Generator Column Method		Not Applicable. Product is not a pure active ingredient.		
830.7950	Vapor Pressure		Not Applicable. Product is not a pure active ingredient.		
Series 870 - Health Effects Test Guidelines, Group A - Acute Toxicity Test Guidelines:					
870.1100	Acute Oral Toxicity	46166103	McLaughlin Gormley King Company	PER	
870.1200	Acute Dermal Toxicity	46166104	McLaughlin Gormley King Company	PER	
870.1300	Acute Inhalation Toxicity		Waiver Requested: Please refer to justification outlined in "Volume 3 of 3 of Submission" entitled: *"Sergeant's Cyphenothrin Squeeze-On for Dogs Waiver Request from the Requirement to Conduct Acute Inhalation Data - 870.1300"*		
870.2400	Acute Eye Irritation	46166105	McLaughlin Gormley King Company	PER	
870.2500	Acute Skin Irritation	46166106	McLaughlin Gormley King Company	PER	
870.2600	Skin Sensitization	46166107	McLaughlin Gormely King Company	PER	

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Agent for Sergeant's Pet Care Products, Inc

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
[redacted]			Not Applicable. Product is not a pure active ingredient.		
			Not Applicable. Product is not a pure active ingredient.		
			Not Applicable. Product is not a pure active ingredient.		
Series 870 - Health Effects Test Guidelines, Group A - Acute Toxicity Test Guidelines:					
[redacted]			McLaughlin Gormley King Company	PER	
			McLaughlin Gormley King Company	PER	
			Waiver Requested: Please refer to justification outlined in "Volume 3 of 3 of Submission" entitled: *"Sergeant's Cyphenonthrin Squeeze-On for Dogs Waiver Request from the Requirement to Conduct Acute Inhalation Data - 870.1300".*		
			McLaughlin Gormley King Company	PER	
			McLaughlin Gormley King Company	PER	
			McLaughlin Gormely King Company	PER	

Signature: Marla K. Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 830 - Product Properties Test Guideline, Group B - Physical/Chemical Properties Test Guidelines - Continued:					
830.7840	Water Solubility, Column Elution Method; Shake Flask Method		Not Applicable. Product is not a pure active ingredient.		
830.7860	Water Solubility, Generator Column Method		Not Applicable. Product is not a pure active ingredient.		
830.7950	Vapor Pressure		Not Applicable. Product is not a pure active ingredient.		
Series 870 - Health Effects Test Guidelines, Group A - Acute Toxicity Test Guidelines:					
870.1100	Acute Oral Toxicity	46166103	McLaughlin Gormley King Company	PER	
870.1200	Acute Dermal Toxicity	46166104	McLaughlin Gormley King Company	PER	
870.1300	Acute Inhalation Toxicity		Waiver Requested: Please refer to justification outlined in "Volume 3 of 3 of Submission" entitled: *"Sergeant's Cyphenothrin Squeeze-On for Dogs Waiver Request from the Requirement to Conduct Acute Inhalation Data - 870.1300"*		
870.2400	Acute Eye Irritation	46166105	McLaughlin Gormley King Company	PER	
870.2500	Acute Skin Irritation	46166106	McLaughlin Gormley King Company	PER	
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Series 870 - Health Effects Test Guidelines, Group A - Acute Toxicity Test Guidelines:					
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Ingredient: Cyphenothrin

Guideline Ref. Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 870 - Health Effects Test Guidelines, Group F - Special Studies Test Guidelines:					
870.7200	Companion Animal Safety	46166108	Sergeant's Pet Care Products, Inc.	OWN	
Series 810 - Product Performance Test Guidelines, Group C - Invertebrate Control Agent Product Performance Test Guidelines:					
810.3300	Treatments to Control Pests of Humans and Animals: *"Efficacy Evaluation Against Adult Cat Fleas (CTENOCEPHALIDES FELIS), Adult Brown Dog Ticks (RHIPICEPHALUS SANGUINEUS), American Dog Ticks (DERMACENTOR VARIABILIS), Nymphal Deer Ticks (IXODES SCAPULARIS), and Adult (AEDES AEGYPTI) Mosquitoes on Dogs."*	46166109	Sergeant's Pet Care Products, Inc.	OWN	
810.3300	Treatment to Control Pests of Humans and Animals	42614501 45086801 44948301 44546601	McLaughlin Gormley King Company	PER	

Signature: Marla K Jackson	Name & Title: Marla K. Jackson Agent for Sergeant's Pet Care Products, Inc	Date: 6/16/2004

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			McLaughlin Gormley King Company	PER	

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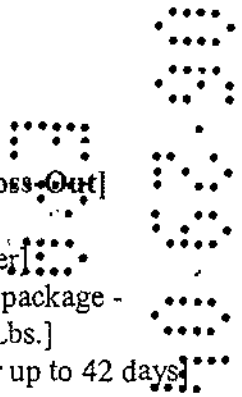
[MASTER CARTON/PACK LABEL - FRONT PANEL]

Sergeant's Cyphenothrin Squeeze-On For Dogs



• **DO NOT USE ON CATS [Box/Icon with Cat Image and Cross-Out]**
[• Pleasant Fresh Scent [or][Fragrance]]
[• Flea & Tick Control for Dogs & Puppies 12 weeks old and older]
[• ?? {?? - dependent on applicator size and quantity in market package - "e.g.3, 6 or 12 Months"} Supply][For Dogs Weighing Up To ?? Lbs.]
[• Three Way Protection [Kills fleas, ticks, and mosquitoes]] [for up to 42 days] [per application]
[•Three Way Protection to [Kills fleas, ticks, and mosquitoes]]
[•3 Way Protection! Kills ticks, & mosquitoes]
[• Extended Protection] [[42-Day] [6 Week] [Flea ,Tick & Mosquito Treatment]
[• 42-Day Flea and Tick Control]
[• For Dogs & Puppies (Over 12 Weeks of Age) Less than 15 lbs.]
[• For Dogs & Puppies (Over 12 Weeks of Age) 15 to 33 lbs.]
[• For Dogs & Puppies (Over 12 Weeks of Age) 33 to 66 lbs.]
[• For Dogs & Puppies (Over 12 Weeks of Age) 66 lbs and Over]
[• Three Applications {for cartons with 3 applicators}.] and/or [4-1/2 Month Supply] or [18 Week Supply]
[• For Dogs [less than 15 lbs.] or [15 lbs. to 33 lbs.] or [33 lbs. to 66 lbs.] or [66 lbs. and Over]
[• Best if used year round!]
[• Kills & Repels Fleas Up to [6 weeks], [42 days!]
[• Kills & Repels New Fleas in less than 1 hour!]
[• Kills & Repels New Ticks in less than 3 hours!]
[• Kills & Repels 95% of Fleas and Ticks [and continues to work for up to six weeks]
[• Kills 99% of Fleas one day after application]
[• Prevents ticks from attaching and feeding within 3 hours after application]
[• 95% efficacy against ticks for up to[6 weeks] [42 days]
[• Kills and Detaches Ticks]
[• Kills over 95% of Ticks]
[• Easy to Use Application]
[• Specially Formulated for Dogs and Puppies]
[• Patented Technology [combines effectiveness with gentleness!]]
[• 42 Day Protection!]
[• Monthly Calendar Stickers Inside!]
[• Kills Mosquitoes for up to [30 days!] [42 days!]
[• Kills Mosquitoes (vector of West Nile Virus) for up to [30 days] [42 days!]

[• Protects Against Blood Feeding by Mosquitoes (vector of Heartworm) For up to [30 days!] [42 days!]
[• Kills & Repels Ticks for Up to [42 days],[6 weeks]!]
[• Kills & Repels Deer Ticks (vector of Lyme Disease) for up to [35 days!] [42 days!]
[• Kills & Repels Ticks (Including Deer Ticks) for up to [35 days!] [42 days!]
[• Kills & Repels Brown Dog Ticks [(*Rhipicephalus sanguineus*)] for up to 42 days!]
[• Kills & Repels American Dog Ticks [(*Dermacentor variabilis*)] for up to 42 days!]
[• Apply every [42 days], [6 weeks]!]
[• 42 Days Flea and Tick Treatment!]
[• Kills & Repels Fleas and Ticks for up to 42 days!]
[• Kills & Repels Mosquitoes that are vectors of West Nile Virus.]
[• Waterproof formula.]
[• Dogs can be bathed 24 hours after squeeze-on is applied]
[• Continues to work 50% longer than other leading brands]
[• Longest lasting, quick acting]

[• May contain graphics illustrating product use, e.g., dog with a drop falling onto its neck from a vial on front, side, or back carton label and/or applicator labeling.]

[ ] - Denotes Optional Statements and/or Images that May be Used on Front, Back or Side Label Panels.

ACTIVE INGREDIENTS:
Cyphenothrin (CAS# 39515-40-7) 40.0%
OTHER INGREDIENTS: 60.0%
TOTAL: 100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See [Back][or][Side] Label Panel[s] for Additional Precautionary Statements

NET CONTENTS: **[THREE][SIX][TWELVE] 1.0 ml Tubes**
[THREE][SIX][TWELVE] 1.5 ml Tubes
[THREE][SIX][TWELVE] 3.0 ml Tubes
[THREE][SIX][TWELVE] 4.5 ml Tubes

[MASTER CARTON/PACK LABEL - BACK/SIDE PANELS]

Sergeant's Cyphenothrin Squeeze-On For Dogs

[DO NOT USE ON CATS] [Box/Icon with Cat Image and Cross-Out]

READ ENTIRE LABEL BEFORE EACH USE.
USE ONLY ON DOGS AND PUPPIES OVER 12 WEEKS OF AGE.
DO NOT USE ON CATS

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS AND DOMESTIC ANIMALS

CAUTION: Harmful if swallowed or absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling. FOR EXTERNAL USE ON DOGS ONLY. Do not use on puppies under 12 weeks of age. Consult a veterinarian before using this product on debilitated, aged, medicated, pregnant, or nursing dogs. Consult a veterinarian before using on dogs with known organ dysfunction. DO NOT USE ON CATS or animals other than dogs. Cats that actively groom or engage in close physical contact with treated dogs may be at risk of serious harmful effects. Sensitivities may occur after using ANY pesticide product on pets. If signs of sensitivity occur bathe your dog with a mild soap and rinse with large amounts of water. If signs continue, consult a veterinarian immediately.

FIRST AID	
If in eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.
If swallowed	• Immediately call a poison control center or doctor. • Do not induce vomiting unless told to do so by the poison control center or doctor. • Do not give any liquid to the person. • Do not give anything by mouth to an unconscious person.
If on skin or clothing	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15-20 minutes. • Call a poison control center or doctor for treatment advice.

HOTLINE NUMBER

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-224-PETS [or][x-xxx-xxx-xxxx] for emergency medical treatment information.

NOTE TO PHYSICIAN OR VETERINARIAN

Treat patient symptomatically

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. DO NOT USE ON CATS. May be toxic and potentially fatal if applied to or ingested by cats.

How to apply: Remove product tube from package. Holding tube with top end pointing up and away from face and body, snap or cut off top end. Invert tube over dog and use open end to part dog's hair. Squeeze tube firmly to apply all of the solution to the dog's skin, as directed below. Repeat application may be made if necessary, but do not apply more often than once every 4 weeks.

For Dogs Weighing 15 lbs. and Under: {For cartons containing 1.0 ml applicator tubes}
Apply one tube (1.0 ml) as a spot or stripe to the dog's back between the shoulder blades.

For Dogs Weighing Between 15 and 33 lbs. {For cartons containing 1.5 ml applicator tubes}
Apply one tube (1.5 ml) as a spot or stripe to the dog's back between the shoulder blades.

For Dogs Weighing Between 33 and 66 lbs. {For cartons containing at least two 1.5 ml applicator tubes, or at least one 3.0 ml applicator tube}
[Apply two tubes (1.5 ml) as a spot or stripe to the dog's back between the shoulder blades and apply the second tube as a spot or stripe to the dog's back directly in front of the base of the tail.] - or - [Apply one tube (3.0 ml) as a continuous stripe on the dog's back starting between the shoulder blades and ending directly in front of the base of the dog's tail.]

For Dogs Weighing 66 lbs. and Over: {For cartons containing at least three 1.5 ml applicator tubes, or at least one 4.5 ml applicator tube}
[Apply the first tube (1.5 ml) as a spot or stripe to the dog's back between the shoulder blades and apply the contents of the other two tubes (1.5 ml each) along the dog's back extending to directly in front of the base of the tail.] - or - [Apply one tube (4.5 ml) as a continuous stripe on the dog's back starting between the shoulder blades and ending directly in from of the base of the dog's tail.]

[MASTER CARTON/PACK LABEL - BACK/SIDE PANELS]

STORAGE AND DISPOSAL

STORAGE: Do not remove tube from the pack until ready to use. Store in a cool (below 25°C) dry place inaccessible to children and pets. Do not refrigerate. Protect from direct sunlight.

DISPOSAL: If empty: Do not reuse this container. Place in trash or offer for recycling if available. **If partly filled:** Call your local solid waste agency or 1-800-CLEANUP for disposal instructions. Never place unused product down any indoor or outdoor drain.

[Sergeant's Cyphenothrin Squeeze-On For Dogs is an effective and easy to use product.] [Sergeant's Cyphenothrin Squeeze-On For Dogs has demonstrated that greater than 95% control of fleas and ticks are killed within one day of application.] [As with all flea and tick control products, Sergeant's Cyphenothrin Squeeze-On For Dogs should be used as part of a program aimed at reducing flea populations in the dog's environment (bedding, carpets, kennel, yard).] [Consult your retailer for program recommendations.]

[www.sergeants.com]

MADE IN USA

[Sergeant's is committed to providing high quality products. If you have questions or comments about this product, please write: Sergeant's Consumer Response; P.O. Box 540399; Omaha, NE 68154-0399.]

[Satisfaction Guaranteed!] [Please return for a refund if not completely satisfied!]

[In Case of Emergency, call 1-800-224-PETS.]

[WARRANTY: SERGEANT'S PET CARE PRODUCTS, INC. MAKES NO WARRANTY OF MERCHANTABILITY, FITNESS FOR ANY PARTICULAR PURPOSE, OR OTHERWISE, EXPRESSED OR IMPLIED, CONCERNING THIS PRODUCT OR ITS USES WHICH EXTEND BEYOND THE USE OF THE PRODUCT UNDER NORMAL CONDITIONS IN ACCORDANCE WITH THE STATEMENTS MADE ON THIS LABEL.]

Made in the USA For:
Sergeant's Pet Care Products, Inc.
Omaha, NE 68130
EPA Reg. No. 2517 -XX
EPA Est. No. XXXXX -XX -XXX

[BAR CODE AREA]

[TUBE/APPLICATOR LABEL]

FRONT PANEL -

Sergeant's Cyphenothrin Squeeze-On For Dogs, [Box/Icon with Cat Image and Cross-Out], [1.0 ml] or [1.5 ml] or [3.0 ml] or [4.5 ml], Active Ingredients: Cyphenothrin 40.0%; Other Ingredients: 60.0%

BACK PANEL -

READ DIRECTIONS/PRECAUTIONS BEFORE USING. CAUTION: KEEP OUT OF REACH OF CHILDREN EPA REG. NO. 2517-XX

Revised 06/16/2004:
S:\Main\Sergeant's Pet Products\Labels\Sergeant's Cyphenothrin Squeeze-On For Dogs.

Pages 127-128*Confidential Statement of Formula may be entitled to confidential treatment*